EXHIBIT 91

Establishment Inspection Report
Actavis Totowa LLC
Totowa, NJ 07512

FEI:
EI Start: 03/18/2008
EI End: 05/20/2008

TABLE OF CONTENTS

SUMMARY

An inspection of this large generic prescription pharmaceutical manufacturer was conducted as a qualifying GMP inspection of a new site (990 Riverview Drive, Totowa, NJ) as per FACTS Assignment 923742, Operation ID 3601487. The inspection provided general GMP coverage. Pre-approval coverage was planned but not conducted. Inspectional coverage was afforded through Compliance Program Guidance Manual 7356.002: Drug Manufacturing Inspections and 7356.021, Drug Quality Reporting System NDA Field Alert Reporting.

The previous GMP and PAI inspection of 9/5/07 et.al., was conducted at the 101 East Main Street Facility located in Little Falls, NJ which has the same FEI number as the new facility at 990 Riverview Drive, Totowa, NJ. The two sites (Little Falls, NJ and Totowa, NJ) were assigned the

same FEI number due to their close proximity and intentions of moving from Little Falls, NJ to Totowa, NJ. The previous inspection of the Little Falls, NJ facility provided coverage of the Quality, Production, Laboratory Control, Materials and Facilities & Equipment Systems. Deficiencies were documented in the areas of Field Alerts, the stability testing program, and investigations. An FDA 483, Inspectional Observations, was issued at the close of the inspection and [redacted] Corrections were promised for all observations. The inspection was classified "VAI".

This inspection was limited to coverage of the Quality System due to significant cGMP deficiencies including but not limited to out of specification in-process, finished product and stability results for more than [redacted] prescription pharmaceutical products; release of Digoxin Tablets, 0.125mg, lot# 70924A2, following visual inspection of the [redacted] to remove "double thick" tablets; failure of the Quality Unit to reject products not meeting specifications, to complete Quality Assurance investigations, to expand investigations to other lots and products, to file NDA Field Alerts within timeframes, and to respond to out of specification products on the marketplace. Analytical methods requiring remediation remained in use and approximately [redacted] prescription drug products had no analytical evaluations of impurities on stability. Written procedures were not followed and changes with potential product quality impact were not all reviewed and approved by the Quality Unit. No market action was taken by the Quality Unit for any products on the market at the initiation of the inspection despite the confirmed out of specification in-process, finished product, and stability results. During the inspection, commitments to recall products were initiated based on inspectional findings. No comprehensive risk assessment or quality evaluation for all products on the market was conducted by the firm's Quality Unit prior to completion of the inspection. No additional systems were covered following the documented Quality System failure. No pre-approval coverage was afforded and the firm was notified that withholds of pending applications were recommended. Documentary Samples were collected to demonstrate interstate commerce and cGMP violations. No refusals were documented during the inspection. An FDA 483, Inspectional Observations was issued on 5/20/08 to Robert Wessman, CEO. Mr. Wessman committed to not releasing any products prior to discussion with FDA, conducting a review of all products remaining on the market, closing open investigations, implementing a new Quality structure, and resuming manufacturing on a product-by-product basis. Commitments to recall finished products from the marketplace were initiated on 4/9/08 and continued throughout the inspection for such products as Digoxin Tablets, Pentazocine and Naloxone Hydrochlorides Tablets, Carisoprodol/Aspirin/Codeine Phosphate Tablets, Hydrocodone Bitartrate and Homatropine Methylbromide Tablets and Multi Vita-Bets pediatric prescription vitamins. However, there is no assurance of the strength, quality and purity of the approximately [redacted] of other products that remain on the market, all lots remaining in the two distribution centers, and the in-process products that remain at the firm's Little Falls, NJ and Totowa, NJ locations. The products were manufactured, tested and released by the same Quality System.

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	03/18/2008
Totowa, NJ 07512	EI End:	05/20/2008

ADMINISTRATIVE DATA

Inspected firm:	Actavis Totowa LLC
Location:	990 Riverview Drive Totowa, NJ 07512
Phone:	973-200-2055
FAX:	
Mailing address:	990 Riverview Drive Totowa, NJ 07512
Dates of inspection:	3/18/2008, 3/19/2008, 3/20/2008, 3/24/2008, 3/25/2008, 3/26/2008, 3/27/2008, 4/1/2008, 4/2/2008, 4/3/2008, 4/7/2008, 4/8/2008, 4/9/2008, 4/14/2008, 4/15/2008, 4/16/2008, 4/17/2008, 4/22/2008, 4/23/2008, 4/29/2008, 5/2/2008, 5/7/2008, 5/8/2008, 5/13/2008, 5/14/2008, 5/15/2008*, 5/20/2008
Days in the facility:	27
Participants:	Erin D. McCaffery, Investigator Kristy A. Zielny, Investigator

**It was noted following the exit meeting that the 5/15/08 inspectional date was inadvertently left off the list of inspectional dates on the FDA 483.*

On 3/18/08, I, Investigator Erin D. McCaffery, presented my credentials and issued an FDA 482, Notice of Inspection (Att) to Mr. Apurva Patel, Managing Director. Mr. Apurva Patel stated he was authorized to receive the Notice and was the most responsible firm official on site. I explained that the purpose of my visit was to perform an initial qualifying GMP inspection for the new manufacturing and testing facility located at 990 Riverview Drive, Totowa, NJ 07512. I noted that pending the outcome of the GMP inspection, pre-approval coverage may also be conducted. Also present for the initiation of the inspection was Anthony Castellazzo, Director Quality Assurance. Mr. Castellazzo contacted Phyllis Lambridis, Vice President U.S. Quality and Compliance who is located at the firm's corporate office in Morristown, NJ. Ms. Lambridis joined the inspection later that morning.

Mr. Apurva Patel, Ms. Phyllis Lambridis and Mr. Scott Talbot, former Site Head of Quality for Actavis Totowa, LLC provided all requested information and documentation and arranged for meetings with additional personnel as necessary throughout the inspection. [redacted], acted as a scribe throughout the inspection.

On 4/3/08, a second FDA 482, Notice of Inspection (Att), was issued and credentials were presented to Mr. Apurva Patel, Managing Director, to add Investigator Kristy A. Zielny to the inspection.

84

On 4/7/08, a meeting was held upon our request with Divya Patel, Executive Chairman, Actavis, LLC, Christopher Young, Director of Solid Oral Dosage for New Jersey, Apurva Patel, Managing Director and Phyllis Lambridis, Vice President U.S. Quality and Compliance to discuss inspectional findings and the lack of response to out of specification products which remained on the market. See also "MEETINGS WITH MANAGEMENT".

At that time, Mr. Divya Patel reported directly to Robert Wessman, CEO. We discussed our inspectional findings including out of specification annual stability batches for multiple products and the failure of the Quality Unit to respond to the results in a timely manner. We explained the need for the information to be provided to the firm's upper management. Mr. Divya Patel assured us that he had fully informed Mr. Wessman and others of our findings and corrective actions were being given the highest priority. We discussed the need to evaluate all products and methods to determine other potential risks. Mr. Young provided a commitment to discontinue a number of products and to stop and remediate a number of other products. We also expressed concern with the analytical methods for which a number of calculation errors were identified as the source of formulation errors and impurity calculation issues.

On 4/9/2008 a written commitment was provided by Ms. Phyllis Lambridis, Vice President U.S. Quality and Compliance (Exh. 12). The letter included [redacted] for which the firm planned to initiate a voluntary recall due to issues such as out of specification assay and impurity results on stability and process related issues. The letter also included a plan to stop and remediate numerous products/processes due to the current cGMP findings. Additional recalls were added to the list throughout the inspection based on inspectional findings and information reviewed by the firm's hired consultants, PAREXEL. The District was formally notified of a probable Class I recall of Digoxin Tablets, 0.125mg, lot# 70924A2 on 4/17/08.

On 4/22/08, a written commitment was provided by Ms. Phyllis Lambridis, Vice President U.S. Quality and Compliance (Exh. 13). The letter committed to ceasing manufacturing and distribution of all "DESI and prescription vitamin products produced at the Little Falls facility as of 4/18/08."

On 4/22/08, we, Investigators Zielny and McCaffery requested interstate documentation for 11 lots of marketed product from Ms. Lambridis. On 4/29/08, Investigators Zielny and McCaffery attempted to collect DOC 419934 for Carisoprodol, Aspirin, and Codeine Phosphate, lot# 60484A1; however the documentation was incomplete. Investigator Zielny continued collection of interstate documentation on 5/2, 7, and 8/08 and affidavits were issued on 5/15/08. The following DOC samples were collected:

DOC 419934: Carisoprodol, Aspirin, Codeine Phosphate Tablets USP, 200 mg/325mg/16mg, Lot # 60484A1

DOC 419935: Digitek (Digoxin Tablets, USP), 0.125 mg, Lot # 70924A1/A2

DOC 419936: Amantadine Hydrochloride Capsules, USP 100 mg, Lot # 60324A1

84

DOC 419937: Phentermine Hydrochloride Capsules USP, 30 mg, Lot # 5704A1
DOC 419938: Oxycodone Hydrochloride Tablets, USP 30 mg, Lot # 80255A1
DOC 467811: Phentermine Hydrochloride Capsules USP, 37.5 mg, Lot # 70996A1
DOC 467812: Betaxolol Tablets, USP, 10 mg, Lot # 60215A1
DOC 467813: Mirtazapine Orally Disintegrating Tablets, 30 mg, Lot # 70421A1
DOC 467814: Digitek (Digoxin Tablets, USP), 0.125 mg, Lot # 71005A1
DOC 467815: Pentazocine and Naloxone Hydrochlorides Tablets, USP, 50mg(base)/0.5mg(base), Lot # 80016A1
DOC 470185: Hydrocodone Bitartrate and Homatropine Methylbromide Tablets, 5mg/1.5mg, Lot # 5683A1

On 4/22/08, an FDA 482, Notice of Inspection (Att) was issued to Apurva Patel, Managing Director at the 101 East Main Street, Little Falls, NJ site. We, Investigators McCaffery and Zielny, presented our credentials to Mr. Patel for the purposes of conducting a walkthrough of the current manufacturing facility.

On 4/23/08, a meeting was held with Investigators Zielny and McCaffery to include Sigurdur Oli Olafsson, Deputy, CEO Actavis Group & CEO Actavis, Inc., Gudrun Eyjolfsdottir, Executive Vice President Quality and Compliance Actavis Group, Phyllis Lambridis, Vice President U.S. Quality and Compliance Actavis Inc., and Jeffrey Rope, Vice President Operations EU Actavis Group to announce changes in management, hiring a third party consultant and reducing the firm's product list to [redacted] chemical entities (approximately [redacted] ANDA/NDA products). See also "MEETINGS WITH MANAGEMENT".

On 4/28/08, a letter detailing the firm's planned organizational changes, the hiring of a third party consultant, PAREXEL, and the rationalization of products was provided by Mr. Olafsson. The presentation given on 4/23/08 was attached to the letter (**Exh. 14**).

On 5/6/08 a letter was provided to New Jersey District by Sigurdur Oli Olafsson, Deputy, CEO Actavis Group & CEO Actavis, Inc. The letter described the firm's intentions to release "Certain Quarantined Lots" following third party review by PAREXEL (**Exh. 15**). The eight product lots released included Oxycodone 15mg and 30mg Tablets and Phentermine 37.5mg Tablets. (See FDA Observations 1, 4d., 6b.)

On 5/14/08, Investigator McCaffery met with Ms. Gudrun Eyjolfsdottir, Executive Vice President, Quality and Compliance, Actavis Group and Ms. Phyllis Lambridis, Vice President U.S. Quality and Compliance, Actavis, Inc. to discuss the upcoming exit meeting. We discussed the general findings since our last meeting with Ms. Eyjolfsdottir on 4/23/08. We also discussed the need for documentation to be provided in a timely manner to the Agency for the recalls and the concerns regarding other lots of products manufactured, tested and released by the same Quality System.

B4

Both Ms. Eyjolfsdottir and Ms. Lambridis acknowledged the severity of the cGMP deficiencies and stated the need for corrective actions, restructuring of the Quality Unit, and hiring.

On 5/15/08, Investigator Zielny met with Daniel Bitler, Director Quality Assurance to review the FDA 463a, Affidavits for the Documentary Samples. See "SAMPLES COLLECTED".

On 5/20/08, an FDA 482, Notice of Inspection (Att), was issued and credentials were presented to Ms. Phyllis Lambridis, Vice President U.S. Quality and Compliance to add Supervisory Investigator Lisa Harlan to the inspection for the exit meeting.

On 5/20/08, an FDA 483, Inspectional Observations (Att) was issued to Mr. Robert Wessman, CEO, Actavis Group. Discussions with management were held throughout the inspection and at the exit meeting prior to issuance of the FDA 483. Corrections were promised for all observations and discussion items. Mr. Wessman promised to provide a written response to the FDA 483 and a letter documenting the commitments made at the exit meeting.

Two commitment letters were provided to New Jersey District Office on 5/20/08 from Robert Wessman, CEO, Actavis Group and on 5/21/08 from Sigurdur Oli Olafsson, Deputy, CEO Actavis Group & CEO Actavis Inc. (Exhs. 16, 17). The letter from Mr. Wessman provided in writing the verbal commitments that he made at the exit meeting to include: discontinuation of release of products manufactured prior to 5/20/08 (FDA will be notified prior to any release); review by a third party of all batches on the market; completion of open investigations; details of a new Quality structure, and a commitment to manufacture products one at a time following a written protocol and after specified corrective actions.

The 5/21/08 letter (Exh. 17) from Mr. Olafsson stated that the firm would provide a separate detailed response to the FDA 483; however the letter was intended to provide an update of the commitments included in the 5/6/08 letter. The letter states that on April 24, 2008, Actavis stopped producing and shipping all products manufactured at Actavis Totowa and PAREXEL had begun evaluating the records for previously manufactured products. The letter then states that they subsequently released lots based on PAREXEL's review from May 1, 2008 until May 15, 2008. The letter commits to not releasing any product manufactured prior to May 20, 2008 without discussion with FDA.

Investigator Erin D. McCaffery was present for the following days of the inspection: 3/18-20, 24-27, 4/1-3, 7-9, 14-17, 22, 23, 29 and 5/13-14, 20/08
Investigator Kristy A. Zielny was present for 4/3, 7-9, 14-17, 22-23, 29 and 5/2, 7-8, 13, 15/08.
Supervisory Investigator Lisa Harlan was present at the exit meeting on 5/20/08.

All sections of this reports were jointly written by Investigator McCaffery and Investigator Zielny.

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	03/18/2008
Totowa, NJ 07512	EI End:	05/20/2008

HISTORY

Actavis Totowa LLC continues to perform operations from three sites. This site, located at 990 Riverview Drive, currently houses the QC laboratory. The second site, which shares the same FEI as the 990 Riverview Drive facility, is located at 101 East Main Street, Little Falls, NJ, and is responsible for all manufacturing operations as well as raw material receiving (**Exh. 26**). The third site is located at 4 Taft Road, Totowa, NJ (separate FEI), and is responsible for all packaging, labeling, distribution, packaging component receiving and R&D. Some Quality Control overflow testing is also completed at the Taft Road Facility as well as the testing of ANDA submission batches.

Actavis Totowa LLC plans to transfer all operations currently at the Little Falls facility to the Riverview Drive site. The 101 East Main Street, Little Falls, NJ facility was visited as part of the current inspection.

Actavis Totowa LLC, previously operated as Amide Pharmaceuticals, Inc., which was founded in 1983. The firm operated under a Consent Decree of Permanent Injunction from 1992 – 2001, when the Consent Decree was lifted. Amide was acquired by Actavis on July 27, 2005. The name legally changed to Actavis Totowa LLC on May 15, 2006. Actavis Totowa LLC is a wholly owned subsidiary of Actavis Group (a privately owned company), which was founded in 1956 and is based in Reykjavick, Iceland. The Actavis Group is a large generic pharmaceutical company, with locations in about 40 different countries (**Exh. 18**). Other U.S. sites include: Morristown, NJ (Corporate Office), Elizabeth, NJ (former Alpharma Purepac site), Windsor, MD (site is planning to close and consolidate with NC site), Lincolnton, NC, and Sunrise, FL (R&D facility).

A Warning Letter was issued to Actavis Totowa LLC, Little Falls, in 8/06 for the manufacturing of unapproved new drug products ("DESI") and failure to comply with ADE reporting requirements.

A second Warning Letter was issued to Actavis Totowa LLC, Little Falls for cGMP deficiencies in 1/07 (revised Warning Letter was sent in 2/07 for the addition of charges regarding the manufacturing and marketing of Ergotamine containing drug products).

All regulatory correspondence should be addressed to Sigurdur Oli Olafsson, Deputy CEO Actavis Group and CEO Actavis, Inc. at 990 Riverview Drive, Totowa, NJ. Mr. Olafsson is currently the most responsible individual at this facility. Robert Wessman, CEO, Actavis Group should also be copied on all correspondence at Dalshraun 1, 220 Hafnarfjordur, Iceland.

The Riverview Drive, Totowa, NJ facility currently operates [redacted] through [redacted], and as needed on weekends. There were approximately [redacted] individuals employed at this facility at the beginning of the inspection. The Riverview Drive facility consists of approximately [redacted] of which will be manufacturing space. A diagram of the

84

facility for Riverview Drive, Totowa, NJ was provided as Exh. 19. The Little Falls, NJ site consists of two buildings: Building A is [redacted] square feet and consists of administration, manufacturing, QA, QC, RA, and warehouse space. Building B was formerly used for packaging and is currently used for quarantined and rejected materials (Exh. 20). It is approximately [redacted] square feet and is being decommissioned but is still used for holding quarantined and rejected goods. The annual volume of sales for Actavis for 2007 was approximately [redacted] No annual sales are reported separately for the Totowa sites.

During discussions of the numerous stability failures, we were notified that the firm had not begun putting products on stability in [redacted] until [redacted] Subsequently, some of the products which were out of specification upon stability testing were attributed to the new temperature and humidity conditions following their [redacted] exposure and inadequate packaging materials. We also observed improvements in the quality of the laboratory data retention and review. Audit trails are routinely evaluated as part of the review process. Additional experienced laboratory staff, dedicated to data review, were trained and perform the raw data review as their sole responsibility, as demonstrated by Manish Patel, Senior Review Chemist at the Riverview Drive, Totowa, NJ facility. The chromatographic system was changed to [redacted] and all HPLC and GC data are collected on the [redacted] erver which is managed by a separate IT function. Historically the firm used stand alone systems, had access to raw data files, and did not maintain all data on a secure server. We noted the increased consistency in data packages that were provided during the inspection and the timely notification by the laboratory to Quality regarding out of specification results. The limited resources of the Quality Assurance group, the lack of oversight of decision making and the failure to respond to product quality issues were all observed as continuing problems during the current inspection despite the improvements in the laboratory.

[redacted]

64

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	03/18/2008
Totowa, NJ 07512	EI End:	05/20/2008

[redacted]

INTERSTATE COMMERCE

Interstate commerce was collected in documentary samples. See "SAMPLES COLLECTED" section of this report. The firm stated that more than [redacted] of their business is in interstate commerce as their two distribution centers are located outside of New Jersey in Louisville, KY and Newark, DE.

JURISDICTION

The firm manufactures prescription pharmaceutical products for approximately [redacted] NDA/ANDA products and [redacted] non-application prescription vitamins and pharmaceuticals. A list of all approved applications and all non-application products was provided as Exh. 21 (This list was modified during the inspection to color code for remediation and discontinuation activities). A list to include the indications for each product was also provided as Exh. 22. A list of products manufactured with controlled substances was provided as Exh. 23.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Organizational charts were provided as Exh. 24.

Robert Wessman, CEO, Actavis Group is the global CEO for Actavis and is located in firm's corporate headquarters in Iceland. He was present at the exit meeting on 5/20/08 and received the FDA 483, Inspectional Observations. Mr. Wessman provided a commitment for corrective action and stated that the other global facilities for which he is responsible are in a state of compliance. He stated that the changes in organization, oversight by a third party consultant, and voluntary recalls were implemented in an effort to remediate the current non-compliance at the facility. Mr. Wessman has been the CEO of Actavis [redacted] He has the responsibility and authority to prevent and correct cGMP deficiencies at the numerous sites that he oversees globally.

Sigurdur Oli Olafsson, Deputy CEO, Actavis Group and CEO Actavis Inc., presented the firm's planned changes in organization, corrective actions, and product rationalization at the 4/23/08 meeting. He explained his new role as the U.S. CEO. He provided commitment letters regarding the use of a third party consultant, PAREXEL, and described plans for remediation and improvement. Mr. Olafsson is now the most responsible person at the Little Falls and Totowa, NJ sites in his new role. He reports to Mr. Wessman, CEO Actavis Group.

B4

Gudrun Eyjolfsdottir, Executive Vice President, Quality and Compliance, Actavis Group reports to Mr. Wessman and is responsible for global Quality. She was present for the 4/23/08 meeting requested by Actavis and was also present on 5/14/08 to discuss inspectional issues and provide a commitment for Quality improvements. Ms. Eyjolfsdottir was not present at the exit meeting.

Jeffrey Rope, Vice President Operations WEMEA/CEEA joined Actavis 5/1/07 and was present at the 4/23/08 meeting and was identified as the new Vice President Operations for Actavis Totowa, 5/08, replacing Apurva Patel. Mr. Rope was moved to the Actavis Totowa facilities to assist in remediation activities including the evaluation of the current manufacturing site at Little Falls, NJ. He provided information regarding equipment and facility changes, reduction in staff due to the discontinuation of numerous products, and changes in management for manufacturing. Mr. Rope described a remediation approach in which products would be evaluated and reintroduced one at a time following corrective actions and product improvements. Mr. Rope will report to Sigurdur Oli Olafsson, Deputy CEO, Actavis Group and CEO Actavis Inc.

Divya Patel, Executive Chairman, Actavis, Inc. is the son of the former owner of Amide Pharmaceuticals. He is located at the Morristown, NJ facility and oversees the U.S. Management board which consists of [redacted] members. Mr. Patel reports directly to Mr. Wessman. Mr. Patel was present on several days of the inspection upon our request.

Apurva Patel, Managing Director is also the son of the former owner of Amide Pharmaceuticals. At the initiation of the inspection, he was the most responsible person at the site on a daily basis. He oversees site operations for the Riverview Drive and Taft Road Totowa, NJ sites as well as the Little Falls, NJ site. He received the FDA 482, Notices of Inspection dated 3/18/08, 4/3/08 and 4/22/08 (Little Falls). Mr. Patel reports to Christopher Young, Director U.S. Solid Oral Dose Operations who is located at the Elizabeth, NJ site (formerly Alpharma/Purepac). Mr. Patel stated that he had worked for Actavis (formerly Amide Pharmaceuticals) for approximately [redacted]. We were notified 4/9/08 that he was leaving the company. This had been announced prior to the inspection.

Phyllis Lambridis, Vice President U.S. Quality and Compliance is located at the Morristown, NJ facility, but has U.S. responsibility for Quality. She has actively participated throughout the inspection as all site quality management at the location are new to the company. Ms. Lambridis joined the company 8/07. She has dual reporting to Mr. Divya Patel, Executive Chairman and Gudrun Eyjolfsdottir, Quality Affairs, Global Head of Quality (Iceland). Ms. Lambridis has the responsibility and authority to notify management of significant quality issues at any of the U.S. sites. She makes quality decisions regarding product recalls, remediation and rejection. She has the authority to release or quarantine batches. We were notified during the inspection that Ms. Lambridis would report directly to Sigurdur Oli Olafsson, Deputy CEO, Actavis Group and CEO Actavis Inc.

B4

Christopher Young, Director U.S. Solid Oral Dose Operations has been with Actavis since 1998. He was promoted to his current role in 2007 and was formerly the Managing Director of the Elizabeth, NJ site. On 4/7/08 he and Divya Patel, Executive Chairman were notified of the Quality System issues. He provided a commitment to reduce the current number of products produced by the site and to evaluate the need for other Operations related corrective actions. Mr. Young reports to Steinthor Palsson, Executive Vice President U.S. Operations.

Richard Dowling, Director Manufacturing Operations Little Falls, NJ participated in the walkthrough of the Little Falls, NJ facility on 4/22/08. He provided information about the ongoing manufacturing activities and provided equipment use logs upon request. Mr. Dowling wrote several of the manufacturing investigations that were reviewed during the inspection. He reported to Apurva Patel, Managing Director, at the initiation of the inspection.

Swapan Roychowdhury, Director Quality Control Laboratory was hired 4/07 as the head of the new Quality Control laboratory at the 990 Riverview Drive, Totowa, NJ site. He provided information during the walkthrough of the laboratory regarding the receipt, analysis, documentation and review of incoming samples to the laboratory. He provided information regarding the move of the laboratory and the plans for method remediation. He discussed out of specification results for impurities and plans for improvements in analytical techniques. We were notified during the inspection that following the hiring of Dorothy Sobczyk, Quality Control Director, that Mr. Roychowdhury was going to become the Director Analytical Services to work on method remediation and development projects.

Jisheng Zhu, Manager Finished Product and Stability Testing is responsible for daily oversight of laboratory operations for finished product and stability testing. Mr. Zhu reviewed numerous Quality Control Laboratory investigations with us throughout the inspection. He provided information regarding the SOPs for investigating out of specification results and suspect test results. He described the laboratory data review procedures and provided laboratory notebooks and raw data upon our request. Mr. Zhu reported to Swapan Roychowdhury, Director QC Laboratory at the beginning of the inspection. We were notified during the inspection that Dorothy Sobczyk, Quality Control Director was hired and Mr. Zhu will now report to Ms. Sobczyk.

Guarang Pandya, Group Leader, Analytical R&D, Actavis, (Taft Road, Totowa, NJ) was present during the inspection to discuss method development and remediation projects. He described the work for such methods as Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (impurities), Amantadine HCl Capsules (assay), Mirtazapine Orally Disintegrating Tablets (impurities), and Guanfacine Tablets (impurities). Mr. Pandya reports to Kirit Patel, Director Analytical Research and Development.

Daniel Bitler, Director Quality Assurance, Totowa, LLC is responsible for overseeing incoming raw materials (including components and labeling), in-process checks in manufacturing and packaging, revision of batch cards for product release, review and approval of validations,

qualifications and change controls and QA investigations as necessary. He is the primary person responsible for the release of product for distribution. He is familiar with production, laboratory and quality activities. He approved numerous Quality Assurance investigations including the investigation into "double thick" Digoxin Tablets. Mr. Bitler assumed his current position in [redacted] replacing Scott Talbot. He reported to Phyllis Lambridis, Vice President U.S. Quality Compliance but currently reports to Anthony Delicato, who was recently named Director Quality Assurance U.S. Solid Oral Dose.

Scott Talbot, Director Quality Assurance U.S. Research and Development (Actavis South Atlantic) was formerly the Site Head Quality from [redacted] He joined the inspection on [redacted] to provide Quality Assurance information since the last inspection. He discussed specific Quality Assurance investigations and facilitated portions of the inspection when Phyllis Lambridis, VP Quality and Compliance was not available. He provided information regarding the Digoxin Tablet investigation and numerous other investigations into analytical method issues, stability out of specification results, and production calculation errors. He discussed the use of retention samples and provided information on Quality Assurance decisions that were made during his tenure. He also [redacted] Mr. Talbot currently reports to Phyllis Lambridis, Vice President U.S. Quality and Compliance and is located at the firm's Sunrise, Florida facility.

[redacted] was reassigned to the new Riverview Drive, Totowa, NJ facility prior to the inspection due to his experience in solid oral dosage manufacturing. He provided information on the walkthrough regarding the new manufacturing facility. He answered questions regarding the compression of Digoxin Tablets which were being manufactured at the new facility as part of the first product transfer. Later in the inspection, we were notified that [redacted] was the new Director of Manufacturing for the Little Falls, NJ facility to assist with the remediation of site prior to transferring any additional products. [redacted] has worked for Actavis since [redacted]

Misbah Sherwani, Senior Manager Quality Assurance Investigations Group, joined the company [redacted] She currently oversees Quality Assurance investigations and complaints for multiple sites including Totowa, Little Falls, and Elizabeth, NJ. She explained the efforts to correct the backlog of incomplete QA investigations and stated that she hoped to hire additional resources. She explained the limitations of the current paper based system to document the QA investigations. She described plans to implement the electronic Trackwise system, which is already in use at the Actavis Elizabeth, NJ site. Ms. Sherwani was also responsible for providing the voluntary recall information to New Jersey District Office. She reports to Phyllis Lambridis, Vice President U.S. Quality and Compliance.

[redacted] She reports to [redacted] She provided initial information about the activities for the planned transfer and validation of Digoxin Tablets to the Totowa, NJ facility from

B4

the Little Falls, NJ site. She also provided the cleaning validation master plan for the new site. Validation activities and the cleaning validation activities for the new facility were not reviewed during this inspection due to the significant cGMP issues identified.

Manish Patel, Senior Review Chemist demonstrated the current laboratory data review and documentation system in the Quality Control Laboratory at Riverview Drive, Totowa, NJ where raw material, finished product and stability testing are conducted. He provided information on the audit trails that were in use during the review process and his role as a data reviewer. He demonstrated the review process of both the notebooks and electronic data. Mr. Patel has been with Actavis for approximately [redacted].

Anthony Castellazzo, Director Quality Assurance, (Riverview) was present at the initiation of the inspection [redacted] He provided information during the facility walkthrough. His responsibilities include quality oversight at the new facility in preparation for the transfer of operations from Little Falls, NJ to Totowa, NJ. He described his role in reviewing qualifications of equipment, facilities, and support systems. Mr. Castellazzo reports to Phyllis Lambridis, Vice President U.S. Quality and Compliance.

[redacted] acted as the scribe throughout the inspection. She took notes and provided copies as requested. She also assisted Mr. Apurva Patel, Ms. Lambridis, and Mr. Talbot in facilitating the inspection.

[redacted]

INSPECTIONAL COVERAGE

The inspection was planned as a qualifying cGMP inspection of the new site [redacted] and pre-approval inspection. Due to the cGMP issues identified, the Quality System was the only system reviewed. The inspection did not include the review of pre-approval applications; however a list of pending ANDA's and supplements was provided as **Exh. 25.** Although a review of the new laboratory was conducted, comprehensive coverage was not afforded due to the significant deficiencies of the Quality System. Limited coverage of validation activities and the manufacturing facilities at both Riverview Drive, Totowa, NJ and East Main Street, Little Falls, NJ were conducted.

ADDITIONAL MEETINGS WITH MANAGEMENT:

4/7/08

On 4/7/08 a meeting was held upon our (Investigators McCaffery and Zielny's) request with Divya Patel, Executive Chairman, Actavis, LLC, Christopher Young, Director of Solid Oral Dosage for New Jersey, Apurva Patel, Managing Director and Phyllis Lambridis, Vice President U.S. Quality

84

and Compliance to discuss inspectional findings and the lack of response to out of specification products which remained on the market. At that time, Mr. Divya Patel reported directly to Robert Wessman, CEO. We discussed our inspectional findings including out of specification annual stability batches for multiple products and the failure of the Quality Unit to respond to the results in a timely manner. We also discussed the incomplete or undocumented Quality Assurance investigations. We explained the need for the information to be provided to the firm's upper management. Mr. Divya Patel assured us that he had fully informed Mr. Wessman and others of our findings and corrective actions were being given the highest priority. We discussed the need to evaluate all products and methods to determine other potential risks. Mr. Young provided a commitment to discontinue a number of products and to temporarily discontinue and remediate a number of other products. We expressed concern with the analytical methods for which a number of calculation errors were identified as the source of formulation errors and impurity calculation issues.

4/23/08

Ms. Lambridis notified us that their corporate management wanted to meet with us to discuss planned organizational changes and corrective actions based on inspectional findings. In a meeting at Actavis 990 Riverview Drive, Totowa, NJ on 4/23/08, the following firm personnel were present:

Sigurdur Oli Olafsson, Deputy, CEO Actavis Group & CEO Actavis, Inc.
Gudrun S. Eyjolfsdottir, Executive VP Quality and Compliance
Jeffrey Rope, VP Operations WEMEA/CEEA
Phyllis Lambridis, VP U.S. Quality and Compliance

Mr. Olafsson stated that the firm would take a three step approach to remediation to include (Exh. 14):

1. Organizational changes effective Monday April 28, 2008

Mr. Olafsson stated that he will move from Iceland and become the CEO of U.S. Actavis (effective 4/23/08). Mr. Jeffrey Rope will move from Ireland and become the Totowa Site Head to replace Apurva Patel, Managing Director. Mr. Patel had previously planned to leave the firm to pursue other business opportunities.

2. Third Party Oversight

PAREXEL Consulting was contracted to conduct quality evaluations and act as a third party oversight of all operations starting the week of 4/28/08. They will evaluate what products will be retained, what corrective actions are needed and will assess all products.

3. Product Rationalization

At the time of the meeting the firm stated that they would continue to manufacture and distribute [redacted] chemical molecules which are used in [redacted] ANDA products.

B4

We stated that due to the numerous cGMP deficiencies identified within the Quality System, there was no assurance of the quality of other products currently manufactured or tested by the site. The products that we evaluated had all been determined to have significant process or method related issues. We stated that a comprehensive evaluation of all processes and methods was needed. We requested any information in support of a quality and risk assessment for the remaining products that were manufactured under the same Quality System and released to the market. No evaluation was provided.

On 4/23/08, following our discussions, we were contacted by Ms. Lambridis who stated that they had decided to stop distribution of all products until further notice. She said that they would await the PAREXEL evaluations and notify FDA prior to releasing and distributing any products. A copy of the presentations provided by Mr. Olafsson was provided in a letter dated 4/28/08 **(Exh. 14)**.

At that time, the firm did not commit to stopping manufacturing despite the numerous product quality issues identified. We, Investigators Zielny and McCaffery observed manufacturing continuing on 4/22/08 during a walk through of the firm's Little Falls, NJ manufacturing facility. Until 4/23/08, when we questioned the quality of all products, they continued to distribute products for which there were known quality issues with the exception of the "recalled" lots.

We stated during the meeting on 4/23/08 our concern regarding the failure of the Quality Unit to respond to the issues identified in laboratory investigations and the failure of the Quality Unit to address manufacturing deficiencies. Although the firm intended to restructure the quality organization and continue hiring, they had difficulty hiring as per Ms. Lambridis. We also discussed our significant concern with the release of Digoxin Tablets 0.125mg, lot# 70924A2, following the findings of "double thick" tablets. The investigation was inconclusive and did not extend to all other lots or strengths of Digoxin Tablets.

MANUFACTURING/DESIGN OPERATIONS

The 990 Riverview Drive, Totowa, NJ 07512 site was intended for transfer of all manufacturing and testing operations from the existing 101 East Main Street, Little Falls, NJ 07424 site. The new facility was given the same Firm Establishment Inventory number and labeler code as requested by a letter dated 6/4/07 from Jasmine Shah, Vice President Regulatory and Medical Affairs, Actavis, Inc. **(Exh. 26)** The new facility is approximately 2.1 miles from the old site. Prior to a qualifying cGMP inspection, the firm moved its Quality Control Laboratory from Little Falls, NJ to Totowa, NJ. Ms. Lambridis stated that firm personnel did not consider the move a change because the two facilities shared the same FEI number. I, Investigator McCaffery requested the firm's correspondence with the District or CDER regarding the plans to move the laboratory prior to a successful cGMP inspection. No documentation was provided. The Quality Control Laboratory began testing raw materials and then subsequently finished products and stability samples beginning approximately 9/25/07. We discussed the potential filing and cGMP issues associated with the move prior to a qualifying inspection.

The new facility is approximately [redacted] square feet and a floor plan was provided as Exh. 19. The site will initially be used for the manufacture of immediate release solid oral dosage forms. At the initiation of the inspection, there were approximately [redacted] employees at the site to include: Shipping/Receiving [redacted] Quality Assurance [redacted] Laboratory [redacted] Facilities/Engineering [redacted] Validation [redacted] Manufacturing [redacted] Regulatory Affairs [redacted] and Finance [redacted] The initial product used for the transfer of manufacturing to the facility was Digoxin Tablets. A list of the batches of Digoxin Tablets manufactured at the Riverview Drive, Totowa, NJ site is provided as Exh. 27. The batches have not been released or distributed.

MANUFACTURING CODES

[redacted] describes the firm's lot numbering system. Apurva Patel, Managing Director explained that they use the term "batch" to describe the material produced by a manufacturing batch record. However, a batch may be packaged into multiple packaging configurations or labeled for a contract customer. The portion of the batch is then called a "lot". The batch number remains the same; however two additional alpha numeric characters are appended to the batch number to indicate a different packaging or labeling configuration for the material. The most common configurations include bottles of [redacted] and blister packs. It was noted that the [redacted] designations do not refer to the same packout. An example of the lot numbering system is as follows:

Lot number [redacted] was manufactured in [redacted] It was the [redacted] batch made and was packaged in bottles of [redacted] which was designated as [redacted]

The firm contract manufactures products for such customers as [redacted] They also contract manufacture and label prescription multi-vitamin products for numerous customers such as [redacted]

PRESCRIPTION PRODUCTS WITHOUT APPROVED APPLICATIONS

During the inspection we discussed the manufacture of prescription products that currently do not have approved applications. The firm provided a list of "CURRENTLY MANUFACTURED DESI PRODUCTS"(Exh. 29) Apurva Patel, Managing Director stated that the firm had discussed the manufacture of such products with the Agency and had discontinued manufacturing of some of the products. A list of discontinued products was provided as Exh. 30. He also stated that some IND work had been initiated. He provided a list of "DESI - PRODUCTS FOR FURTHER REGULATORY FILING" (Exh. 31). Mr. Patel stated that the vitamin products historically were treated as "nutritionals" or "dietary supplements". Investigator Zielny asked Mr. A. Patel why the

84

firm continued to manufacture "DESI" products without an approved application. He stated that the "DESIs" that are still being made are either nutritional prescription vitamins or have INDs filed or being filed to support continuing manufacturing. We provided a copy of a letter dated 8/23/08 to Mr. A. Patel from the Agency (Att). We requested the firm's written response which was dated 9/27/07 (Exh. 32). The response indicated that although they discontinued [redacted] products over the last three years, they would continue to manufacture other prescription products and prescription vitamins without approved applications despite the warnings provided in FDA's correspondence to the firm dated 8/23/07.

On 4/17/08, we asked Ms. Lambridis if this remained the company's position on the "DESI" products including prescription vitamins. She stated that she would have to review the information and get back to us. We also observed that the [redacted] currently manufactured prescription vitamin products have full analytical testing performed at release of the product, but many of the components of the vitamin products are not tested on stability to assure that they meet label claim throughout their expiry (Exh. 5d1). (See FDA 483 observation 5d.) On 4/22/08, Ms. Lambridis provided us with a written commitment to discontinue [redacted] "DESI" products and to cease manufacturing of the remaining [redacted] products until remediation is performed (Exh. 13). Additional application product commitments were also contained in this letter. We requested copies of labeling for all prescription vitamin and "DESI" products. A CD-R was provided by the firm to include all product labeling and was submitted during the inspection to CDER Office of Compliance (Exh. 33).

It was also determined during the inspection that approximately [redacted] prescription products including the "DESI" and prescription vitamin products lacked impurity testing on stability (Exh. 3h11). (See FDA observation 5b.) We asked what assurance the firm had of the safety and efficacy of the products in the absence of testing for all ingredients and impurities on stability. Ms. Lambridis stated that she could not provide that assurance and therefore provided a commitment to recall all [redacted] products on the list including all "DESI" and prescription vitamin products. New Jersey District Recall Coordinator was formally notified of the recall on 5/19/08.

COMPLAINTS

Complaints, medical inquiries, and suspect adverse drug event reporting are handled by the firm's Elizabeth, NJ facility and were covered as a separate establishment inspection. All complaints or drug safety issues that are received directly by the firm's Totowa facilities are forwarded to the Elizabeth, NJ site and are processed. If investigations are required at the Totowa facilities, they will be requested by the Elizabeth, NJ site. [redacted] dated 1/3/08 (Exh. 34) was reviewed and does not require the initial logging of the complaints, inquiries, or suspect adverse drug events by the Totowa, NJ site prior to forwarding the information to the Elizabeth, NJ site. We discussed the need for accountability of both sites for the information and the criticality of processing adverse drug events within timeframes. Apurva Patel, Managing Director agreed that a log should be established to account for all complaints received directly by the site. He noted that investigations or other follow-up activities requested by Elizabeth, NJ would follow current SOPs.

64

RECALL PROCEDURES

[redacted] (Exh. 35) was provided as the firm's current procedure for recalls. The procedure indicates that, "a voluntary product recall may be initiated" when it is determined that, "any distributed product is in violation of the FD&C Act." We discussed the firm's failure to react to out of specification in-process, finished product, and stability results throughout the inspection. No market action was taken on any of the associated products on the market until interstate documentation was requested for the following four products:

- Carisoprodol, Aspirin and Codeine Phosphate 200/325/16mg (See FDA 483 observations 1, 3a, 8b, 9a, 11c) [redacted]
- Pentazocine and Naloxone Hydrochlorides Tablets USP, 50mg/0.5mg (See FDA 483 observations 1, 2b, 8a) [redacted]
- Guanfacine Tablets, USP 1mg and 2mg (See FDA 483 observations 1, 3e, 9a) [redacted]
- Muliret Folic 500mg Tablets (See FDA 483 observations 1, 3i, 8d) [redacted]

We, Investigators McCaffery and Zielny, were then notified verbally during the inspection of the commitment to voluntarily recall several of the products for which we had discussed out of specification results or manufacturing problems. Commitments for additional voluntary recalls were made during the inspection based on inspectional findings and findings by the firm's hired consultants, PAREXEL. The formal notifications to the New Jersey District Recall Coordinator were received via e-mail and are summarized in (Att).

The recalls also include a potential Class I Recall for Digoxin Tablets, 0.125mg and 0.250mg due to findings of "double thick" tablets during the packaging process. The Quality Unit approved the visual inspection of the [redacted] and found additional "double thick" tablets. No root cause was identified and evaluations of other lots or strengths were not conducted for this cardio tonic, narrow therapeutic index drug. The recall included [redacted]

At the exit meeting we, Investigators McCaffery and Zielny, informed Robert Wessman, CEO that although they had notified us of the commitment to recall on 4/4/08, for the [redacted] and throughout the inspection for numerous other products, the recall letters were not sent until approximately one month later following our inquiry of the dates the final letters were sent.

B4

Additionally, despite the 10-day timeframe to provide recall information to the FDA following notification of a voluntary recall, no completed recall packages for any of the recalls had been provided at the time of the exit meeting on 5/20/08. Phyllis Lambridis, Vice President Quality and Compliance U.S. acknowledged the delay. Mr. Wessman stated that they would provide the information to the FDA by 5/23/08 in a written commitment provided on 5/20/08 following the exit meeting. Only [redacted] packages were received on 5/23/08.

On 5/30/08, New Jersey District Recall Coordinator was notified by Ms. Lambridis that some lots were omitted from the original recall letters and a second mailing was sent to the consignees. No additional information about the omissions or the date of the resent letters was available at the time of this report.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

At the exit meeting on 5/20/08 discussions with management were held prior to the issuance of the FDA 483, Inspectional Observations (see "DISCUSSIONS WITH MANAGEMENT"). Following the discussions with management, the FDA 483, Inspectional Observations was issued to Mr. Robert Wessman, CEO Actavis Group. Also in attendance were:

- Sigurdur Oli Olafsson, Deputy to the CEO and newly appointed CEO for Actavis U.S.
- Jeffrey Rope, former VP Operations WEMEA/CEEA and newly appointed Head of U.S. Operations Totowa, NJ
- Phyllis Lambridis, Vice President Quality and Compliance U.S.
- [redacted]

FDA was represented by Investigator Erin McCaffery and Supervisory Investigator Lisa Harlan.

Observations listed on form FDA 483

Quality System

OBSERVATION 1

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically,

64

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	03/18/2008
Totowa, NJ 07512	EI End:	05/20/2008

The Quality Unit routinely failed to document, investigate and address product quality issues at the time of occurrence including in-process, finished product and stability out of specification analytical results. There is no assurance that the Quality Unit has the procedures, personnel, or systems to adequately evaluate the quality or validation status of the approximately [redacted] ANDA/NDA products and [redacted] non-application prescription products that they can currently manufacture and release to the market. The impact on finished product quality on the marketplace was not evaluated despite the confirmed out of specification results for at least [redacted] different marketed prescription products evaluated.

At the initiation of the inspection, despite the known product quality issues including, but not limited to in-process, finished product and numerous stability out of specification results, the Quality Unit failed to document, investigate or address product quality issues. There were no products recalled from the market at the time of inspection despite the out of specification stability results for at least [redacted] different marketed prescription products. Quality Assurance investigations were not documented and/or not completed, reviewed or approved at the time of the findings. Additionally, decisions for finished product release were not supported by scientific rationale and investigations of deviations were not reviewed by multiple personnel in the Quality Unit for concurrence. The paper based systems for documenting laboratory, manufacturing and quality investigations were not managed, trended or correlated to determine the comprehensive impact on marketed product. Written procedures were not followed and staffing was insufficient to support the large number of quality investigations required based on the laboratory findings.

The firm manufactured, analyzed and released products without adequate Quality System infrastructure to support them. Additionally, practices such as the testing of retention samples which were not stored in controlled room temperature conditions were used to try to overcome out of specification stability results, but often resulted in additional failures. Market action was not taken for products in which multiple annual stability batches were out of specification. Analytical methods which required remediation were not corrected in a timely manner. There were no impurity specifications on stability for approximately [redacted] prescription non-application products ("DESI" and prescription vitamins). Risk assessments and health hazard evaluations were not conducted by the Quality Unit and changes in formulations were not challenged scientifically or analytically resulting in numerous lots of both over and under formulated product.

Promised corrective actions have addressed specific product quality issues identified on the inspection, but have failed to address the restructuring of the Quality System to prevent further cGMP deficiencies and the other products that were manufactured, analyzed and released by the same failed Quality System. CEO, Robert Wessman was notified of all findings at the FDA 483 exit meeting on 5/20/08. Although the firm had discontinued manufacturing, they had resumed distributing product based on a paper review by their hired consultants. At the time of the exit meeting [redacted] batches were released to market despite the lack of a completed assessment of the firm's systems and previously produced products on the market.

84

Mr. Wessman stated that they would discontinue the release of all products until further discussions were held with FDA. He also reiterated a prior commitment to recall the "DESI" and prescription vitamin products identified during the current inspection due to the lack of impurity testing and approved applications.

We, Investigator McCaffery and Supervisory Investigator Harlan, stated that due to our inspectional findings, in which issues in manufacturing, testing, releasing and investigating products were not adequately documented and not documented at the time of occurrence, that we could not assure that the additional paper review supported the release of the products. We noted our concern for the products that remained in the warehouse and on the market which were produced under the same conditions. Mr. Wessman stated that the consultants would be asked to prioritize the review of these products first.

Reference: 21 CFR 211.22(d)

Supporting Evidence and Relevance:
See FDA observations 2-11 to demonstrate examples of Quality System deficiencies.

OBSERVATION 2

Drug products failing to meet established specifications and quality control criteria are not rejected.

Specifically,

a. **During the packaging of Digoxin Tablets 0.125mg, lot# 70924A1, [redacted] double thick tablets were observed. Quality Assurance approved a 100% visual inspection of the [redacted] million tablet lot which resulted in an additional [redacted] double thick tablets. Although Quality Assurance was aware of the "double thick" tablet findings, the batch was then released based on AQL sampling which included visual inspection of [redacted] tablets. No additional thickness testing or analytical evaluation of the double thick tablets was conducted. No root cause was determined for the defect; however the lot was released to the market by the Quality Unit on 1/28/08 following the visual inspection. There was no documented evaluation of the approximately [redacted] lots that remained on the market at the time of inspection.**

Review of [redacted] (Exh. 2a1 p. 1) revealed that during the packaging of the batch on 11/30/07 [redacted] "Two tablets of Digoxin tablets 0.125 mg were found with approx. double the thickness from counter channels during packaging/filling operation on packaging line [redacted]. According to the batch record (Exh. 2a2 p. 75) and the investigation, the lead operator observed the "double thick" tablets

84

during the packaging of bucket numbers [redacted]. The [redacted] and [redacted] were notified. The Director of Packaging instructed the operator to stop immediately. The [redacted] were notified. (Exh. 2a1 p. 1) The operators were then instructed to perform a [redacted] inspection (visual) of the tablets from the hopper [redacted] as well as the two subsequent buckets [redacted]. One additional "double thick" tablet was found in bucket [redacted] by visual inspection and no thick tablets were observed by visual inspection in bucket [redacted]. The incident report in the batch record notes, "Inspection was completed on 12/1/07 at about [redacted]. Only one thick tablet was found from [redacted] QA supervisor, Aida Ruiz was contacted and with her permission the production was resumed to complete the packaging run with watchful eye on counter." (Exh. 2a2 p. 75) The [redacted] notes, "The remainder of the batch was packaged while operators performed a continuous manual inspection of the tablets as they traveled down the bottle filler channels. While inspecting the final bucket, numbe[redacted]more tablets were identified; bringing the total to [redacted] tablets with double the thickness." (Exh. 2a1 p. 3)

As per the batch record, the batch was placed on hold on 12/5/07 (Exh. 2a2 pp. 97-98). The batch record also contained an "Inspection Protocol" which was approved by the [redacted] (Exh. 2a2 pp. 88-89). The protocol described the following: "This inspection is being performed to ensure that all defect tablets have been removed from the batch. The type of defect to be inspected for will be reviewed with the inspectors. All tablets that are found to be double the thickness will be reported and rejected. Upon completion of this protocol, an AQL sample protocol will be written for Quality Assurance to evaluate the effectiveness of the [redacted] (Exh. 2a2 pp. 88-89). The protocol also noted, "[redacted] will be conducted at the Taft Road facility. Since the tablets have already been packaged, the bottles will need to be emptied and the bulk tablets [redacted] inspected. A total of [redacted] count tablets have been packaged which equates to [redacted]. The findings were included on the "On Line Production Inspection Form." (Exh. 2a2 p. 93) They indicate that, "[redacted] with Approx. double the thickness were removed during inspection of this batch. The removed tablets are attached with this protocol." The findings are dated 1/18/08. I, Investigator McCaffery, asked Ms. Lambridis and Scott Talbot, Director Quality Assurance U.S. Research and Development, (former Director of Quality Assurance at Little Falls, NJ), to see the "double thick" tablets, but was told that they were discarded. No analytical testing or thickness testing was performed on the defective tablets. I discussed the lack of assurance that all tablets with the incorrect thickness and therefore potency were removed due to a "visual inspection." I also discussed the firm's attempt to inspect the batch into compliance. The [redacted] was reviewed and approved by the [redacted] He initialed and dated all attachments and pages of the investigation on 1/25/08 (Exh. 2a1 p. 2).

The investigation focused on compression of the product. It included a review of the compression records which revealed a stop of press [redacted] of compression. The upper

84

and lower punches of the press were removed and cleaned due to, "excessive dust build up on the third day of processing, 11/19/07." A new start-up was required following the removal of the punches. It was theorized by the Manufacturing Manager that, "tablets found with double the thickness might have been produced during the readjustment at start-up. The possibility that tablets might have gotten stuck in the tablet deduster or metal detector and went unnoticed by the press operator is being considered a possible root cause of the tablets found with double the thickness." **(Exh. 2a2 pp. 3-4)** I questioned the theory of "double thick" tablets at the time of the restart of [redacted] because additional tablets were found in [redacted] near the end of the run and [redacted] were found by inspection, but not correlated to a particular time in production. I asked Mr. Talbot if it was typical for an operator to restart a previously set press at "double" the thickness. I also asked if the startup material was the reason for the out of specification tablets, why they were only looking for "double thick" tablets when there might be tablets that varied in thickness. Mr. Talbot agreed that startup material would not be just "double thick tablets" and also noted that an operator would not necessarily start at double the thickness when resetting the tablet press.

The manufacturing department conducted a batch record review of the [redacted] tablet batch; however, it was limited to the compression of the batch. The product was manufactured using [redacted] tablet presses [redacted] It was noted in the batch record that [redacted] are sampled every [redacted] minutes from each chute of each tablet press and checked for thickness as compared to the product specifications [redacted] **(Exh. 2a2 p. 25)**. The manufacturing investigation revealed that [redacted] batch were checked for thickness and were within specification. As per the batch record, the operator also checks the [redacted] for hardness and [redacted] "aggregate weight and appearance." **(Exh. 2a2 p. 25)** No deviations were noted. The batch record contains notes of the stop and restart on 11/19/07; however it seems that the equipment is stopped at [redacted], restarted at [redacted] and then there are additional notations that the machine was stopped and started for QA approval at [redacted] The only QA approval for startup on [redacted] **(Exh. 2a2 p. 28, 37-38)**.

As per the batch record, Quality Assurance takes [redacted] from each exit chute [redacted] station of the press), "at start-up and periodically takes samples while in process to verify weight, thickness, and hardness of each sample." Review of the executed batch record revealed that the start-ups, thickness, hardness and weight checks by QA are documented as **Exh. 2a3 pp. 35-58.**

The investigation did not evaluate the possibility of sticking problems, formulation problems, equipment/tooling problems, operator error, metal detector or deduster problems or other potential sources of "double thick" tablets. No explanation was provided for the failure to chemically analyze the tablets or to evaluate the thickness or weight of all tablets to determine a root cause. I asked Ms. Lambridis and Mr. Talbot how they could assure that other tablets within the batch were not out of specification when the routine checks by the operator and Quality Assurance did not identify the defect, as evidenced by the double thick tablets being found during packaging. Ms. Lambridis and Mr. Talbot could not provide any evidence to assure that additional out of specification tablets would not be identified if inspection by thickness, weight,

84

or chemical analysis was conducted. We also discussed the failure to evaluate other lots and strengths due to the lack of root cause for the defect.

We noted during a review of the record for repackaging of the product that the initial lot, [redacted] resulted in [redacted] (Exh. 2a2 p. 136). Following the inspection process, the product was repackaged as [redacted] and resulted in [redacted] (Exh. 2a2 p. 138). We noted the discrepancy and stated that despite the removal of the [redacted] double thick" tablets found and the AQL sampling, there was an additional bottle of 1000 tablets that resulted. We discussed the finding with Scott Talbot and asked if the discrepancy was investigated. He stated that it was not. He noted that perhaps the counts were within tolerance but slightly different than the first packaging run for the product. No further explanation was provided.

The visually inspected, repackaged product was released by the Quality Unit on 1/28/08 [redacted] (Exh. 2a3 p. 6). A documentary sample, DOC 419935 was collected to document the cGMP deficiencies observed for the product.

Digoxin Tablets are indicated for use as a "cardio ionotropic and anti-arrhythmic agent indicated for the treatment of mild to moderate heart failure" (Exh. 2a4 p. 1. They are taken daily and are considered a low dose product with a narrow therapeutic index. The product is contract manufactured for [redacted] A health hazard evaluation was not conducted at the time of inspection, but was generated on 4/18/08 by a contractor [redacted] hired by Actavis Medical Affairs to "evaluate the impact of Digoxin Tabs 0.125mg that were had a thickness approximately double to that required." (Exh. 2a4 p. 1) The clinical conclusion by [redacted] the health hazard evaluation is as follows:

"Potential risks to the patient depend on the constituency of the tablets. If the tablets contain double the dose (0.250mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy." (Exh. 2a4)

Investigator Zielny and I, Investigator McCaffery, notified New Jersey District Management of the findings during the inspection due to the potential health hazard associated with patients receiving Digoxin Tablets with double the thickness. We also notified the firm's upper management in a meeting on 4/23/08 regarding the firm's plans for organizational changes and corrective actions. Following the meeting, the documentation of the commitments was provided (Exh. 14). Following discussions with CDER's Office of Compliance, District Management contacted Robert Wessman, CEO Actavis Group on 4/24/08 to discuss the potential impact on

B4

other lots of Digoxin Tablets on the market. Mr. Wessman provided a verbal commitment to recall all lots of Digoxin 0.125mg and 0.250mg Tablets on 4/24/08. There were [redacted] of Digoxin 0.250mg Tablets on the market at the time of the recall.

b. **Pentazocine and Naloxone Hydrochlorides Tablets, USP, 50mg (base)/0.5mg (base) were manufactured with an overage of approximately 9% Naloxone Hydrochloride. The master batch record, "incorrectly corrected" the moisture content for the Naloxone HCl Dihydrate which led to the overage for batches manufactured from 9/8/05 until 3/25/08. Additionally, the laboratory practice was to dry the in-house standard for Naloxone HCl Dihydrate, however the method did not correct for drying the standard so the analysis did not reveal the overage. The Quality Assurance investigation was incomplete at the time of inspection despite the known manufacturing overage. There was no documented evaluation of the approximately [redacted] batches that remained on the market at the time of inspection.**

[redacted] out of specification assay results for Naloxone, [redacted] were obtained as documented in laboratory investigation [redacted] (Exh. 2b1 p. 4) and representative laboratory notebooks (Exhs. 2b2-2b11). There was no completed Quality Assurance investigation. An "interim report" to [redacted] was a one paragraph memo with a date of initiation of 1/29/08. In the "REASON FOR EXTENSION" dated 3/20/08, the memo noted, "Root cause has been determined to be an overcharge of Naloxone as the amount presented on the Master Formula Sheet of the Master Production Record has been corrected for moisture. However, the MPR further requires the correction for moisture, resulting in overcharge. A review of all lots manufactured since the effective date of the MPR is currently being conducted and all lots are being calculated correctly to determine the scope." The target completion date for the activity was [redacted] (Exh. 2b12).

The label claim for Naloxone in the drug product is 0.5mg Naloxone base (See DOC 467815). The raw material used to make the product is Naloxone Hydrochloride Dihydrate, so a molecular weight conversion is required to determine the amount of Naloxone HCl Dihydrate needed to deliver [redacted] of Naloxone base. An addition of [redacted] of Naloxone Hydrochloride Dihydrate per tablet results in [redacted] of Naloxone base. Review of the [redacted] included the conversion between the label claim and the raw material (Exh. 2b13 p. 3). As per Mr. Zhu, low, (but within specification), assay results obtained 8/24/05, led to the change in the formula (Exh. 2b25). The low assay results were thought to correspond with an error in the calculation to account for the moisture content associated with Naloxone Dihydrate. [redacted] dated 9/1/05-3/25/08 therefore required an additional correction for the moisture content as noted in each MPR (Exhs. 2b14 p. 3-4, 2b15 p. 3-4, and 2b16 p. 3-4). The additional moisture correction states, "Calculate the quantity of Pentazocine Hydrochloride, USP (B), Naloxone Hydrochloride Dihydrate, USP (D) and Microcrystalline Cellulose, 102, NF (E) based on moisture content of Pentazocine base and Naloxone base. Refer to Page# 2 for calculations."

B4

Change contro[redacted]ocuments the original "incorrect" moisture correction which was reviewed and approved by the Manufacturing Director, Quality Control Director, Regulatory Affairs Director and Quality Assurance Director dated 9/8/05 (Exh. 2b17). The moisture had already been corrected for the batch based on the molecular weight conversion, so the second correction resulted in an overcharge of approximately [redacted] for all batches manufactured using [redacted] Following the finding, the MPR was changed back in [redacted] remove the calculations of Pentazocine Hydrochloride, USP, Naloxone Hydrochloride Dihydrate USP and Microcrystalline Cellulose, 102, NF (Exh. 2b18 p. 1). Although the Master Production Record was changed back in Revision 8, dated 3/21/08 (Exh. 2b18) to remove the incorrect calculation in Change Control [redacted] (Exh. 2b19), no corrective actions were taken regarding the lots on the market with a known manufacturing overage of approximately [redacted] A list of batches on the market within expiry which were manufactured with the Naloxone overage was provided as (Exh. 2b20).

I, Investigator McCaffery, asked Ms. Lambridis why testing of the product did not reveal the overcharge of Naloxone. A draft follow-up to the incomplete [redacted] was provided (Exh. 2b21 p. 1). It included a notation stating, "...the current lab practice was to dry the in-house standard Naloxone HCl Dihydrate, but the conversion factor was not corrected for dried standard in the MOI." The analytical method, [redacted] and [redacted] (Exh. 2b22 p. 4) was provided to show that the method did not require drying of the standard, however it was the "lab practice" to dry it as seen in Exh. 2b5 p. 2 (laboratory notebook). The conversion factor used in the method was not corrected for drying of the standard (Exh. 2b22 p. 14) and therefore did not reveal the overage of Naloxone in the batches. The draft follow-up to the incomplete [redacted] also includes recalculations of the batches for Naloxone assay. (Exh. 2b22). The out of specification assay values and Acceptance Values are bolded and there are many individual content uniformity results which are greater than [redacted] No health hazard evaluation was conducted at the time of inspection. Scott Talbot, Director Quality Assurance U.S. Research and Development, (former Site Head Quality Actavis Totowa, LLC), stated that because Naloxone is used to prevent abuse of the product, they did not consider it an active pharmaceutical ingredient. We stated that the product is labeled as 0.5mg Naloxone base; however it was over-formulated with Naloxone by approximately [redacted] He stated that he understood the cGMP concern. We also discussed with Mr. Talbot and Ms. Lambridis the failure to respond to the finding in a timely manner and to evaluate the potential risk to the patient based on the overage. During the inspection, a "Toxicity Calculation" was provided to demonstrate that the overage was below the [redacted] for Naloxone (Exh. 2b23). Due to the lack of completed QA investigation at the time of inspection, we requested a summary of the issue which was provided as Exh. 2b24. It was also noted while reviewing the documentation that a test of the retention sample [redacted] was also out of specification for assay [redacted] (Exh. 2b12 pp. 16, 17, 26). DOC sample 467815 revealed that the product is contract manufactured for Sanofi Aventis. On 4/4/08, New Jersey District Recall Coordinator was notified that all [redacted] lots remaining on the market were being voluntarily recalled.

84

Establishment Inspection Report	FEI:	2244683
Actavis Totowa LLC	EI Start:	03/18/2008
Totowa, NJ 07512	EI End:	05/20/2008

Reference: 21 CFR 211.165(f)

Supporting Evidence and Relevance:
Observation 2a: 2a1-2a4, 14
Observation 2b: 2b1-2b24

OBSERVATION 3

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically, the following products do not meet finished product or stability specifications throughout the products marketed expiry:

a. **Out of specification assay results for Codeine Phosphate at the 12-month [redacted] and 18-month [redacted] stability stations were obtained on 8/21/07 and 1/16/08, respectively for Carisoprodol, Aspirin and Codeine Phosphate 200mg/325mg/16mg Tablets, lot# 60484A1, an annual stability lot. [redacted] retention samples were also out of specification for assay of Codeine Phosphate or Carisoprodol for lot#s 51044A1, 60121A1, 61024A1 and 5136A1. Although QA investigation 07-042, (initiated 7/20/07 and approved 11/9/07), revealed a manufacturing problem resulting in variability of the tablet bilayers for lot# 70484A, [redacted], the QA investigations for the stability out of specification results were not completed. There was no evaluation of the approximately [redacted] batches on the market at the time of inspection and no evaluation of other bilayer products.**

Firm management was notified that this observation was previously cited during the [redacted] inspection due to the [redacted]. The 12-month [redacted] stability out of specification stability results for assay of Codeine Phosphate [redacted] (Exh. 3a1), laboratory notebook (Exh. 3a2), and draft QA investigation [redacted] (Exh. 3a3) document the confirmed stability failure at the 12-month timepoint which occurred 8/21/07. Although the draft QA investigation references, "A root cause for the bi-layer issue considered the point of production when the compressed tablet samples are taken, sighting that the problem likely occurs at the end of the production run when the hopper is almost empty for one of the two layers." The unsigned draft also includes, "A root cause for the subject deviation was determined to be that the batch was impacted by the degradation and hydrolysis of the Aspirin layer to form Salicyllic Acid." (Exh. 3a3 pp. 3-4). An extension for [redacted] after the original out of specification stability results, with a target completion date of [redacted] stating, "Additonal assessment of impact on marketed lots is

B4

necessary to closeout investigation. Determine how many in-date lots are currently on the market." (Exh. 3a4). The lot was tested on [redacted] timepoint and again was out of specification for Codeine Phosphate [redacted] (Exh. 3a5). The laboratory notebooks (Exh. 3a6), chromatograms (Exh. 3a7), and an addendum to the laboratory OOS investigation [redacted] (Exh. 3a8) document the second out of specification result for the annual stability batch.

We discussed the failure of the Quality Unit to respond in a timely manner to the stability out of specification results and inquired about the cause of the failures due to the incomplete QA investigations and the [redacted] batches on the market (Exh. 3a9). Scott Talbot, Director Quality Assurance, U.S. Research and Development discussed a production issue with the manufacture of the bi-layer tablets. The bi-layer product is not produced with a bi-layer press. It is manufactured using a double-sided press. During the investigation of an Acceptance Value out of specification result obtained [redacted] as documented in OOSN investigation 07-067 (Exh. 3a10) and [redacted] (Exh. 3a11), a manufacturing problem was identified for the production of the bi-layer tablets and included information regarding weight variation of the bilayers dated 8/3/07 (Exh. 3a11 pp. 34-37). Mr. Talbot noted in QA investigation 07-042, "Based on the data attached, there is variability in the proportion of the two active ingredients, this variability has resulted in some of the bi-layers to be out of the finished product specification...The lot will be rejected." (Exh. 3a11 p. 4)

Despite the annual stability out of specification results found on 8/21/07 and the bi-layer manufacturing issue identified in [redacted] initiated 7/20/07 and approved 11/9/07, no market action was taken for the product at the time of inspection.

The testing of [redacted] retention samples was conducted as a follow-up to the investigation of [redacted] The results of the retention sample testing are summarized in OOSN 07-101 Addendum (Exh. 3a12). Four of the [redacted] retention samples were out of specification: (low assay) [redacted] for [redacted] The reported out of specification retention sample data is summarized as the shaded results in Exh. 3a13. The raw data from the laboratory notebooks is included as Exh. 3a14 (initial), Exh. 3a15 (repeat), Exh. 3a16 (additional repeat tests).

The process validation for Carisoprodol/Asiprin/Codeine Phosphate Tablets 200mg/325mg/16mg dated 4/26/99, does not include evaluations of the individual bi-layer weights for the product. It only evaluates total tablet weight (Exh. 3a17 pp. 4, 27, 29-31 and 49-58). Despite the manufacturing issues determined for Carisoprodol/Aspirin/Codeine Phosphate Tablets, the firm continued to produce bi-layer products including Carisoprodol/Aspirin Tablets 200mg/325mg. The Master Product Records were not put on hold until 2/29/08 and 4/7/08, respectively (Exhs. 3a18 and 3a19). The last batch of Carisoprodol/Aspirin/Codeine Phosphate Tablets was started on 8/20/07 and was released on 10/4/07 (Exh. 3a20). The last batch of Carisoprodol/Aspirin Tablets was started 8/7/07 and was released 9/7/07 (Exh. 3a21). Ten batches of Carisoprodol/Aspirin/Codeine Phosphate Tablets and [redacted] of Carisoprodol/Aspirin Tablets were on the market. On 4/4/08 and 4/9/08, respectively, the firm committed to voluntarily recalling these lots.

64

b. **An out of specification assay value for Phentermine HCl [redacted] was obtained on 7/25/07 at the 24-month [redacted] point for Phentermine HCl Capsules, 30 mg, lot# 5436A1, an annual stability lot. QA Investigation 07-066 concludes, "No other batches are impacted by this stability failure." A second stability out of specification assay result, [redacted], was obtained on 12/3/07 at the 2 [redacted] stability time point for Phentermine HCl Capsules, 30mg, lot# 5704AQ. There was no evaluation of the approximately [redacted] batches on the market at the time of inspection.**

The laboratory investigation, [redacted] documented the out of specification (high) assay results at the [redacted] RH stability timepoint, [redacted] (Exh. 3b1). The laboratory notebooks (Exh. 3b2) and chromatograms are included for the original out of specification results (Exh. 3b3). Remeasurement confirmed the initial results (Exh. 3b4). Repeat test results for assay were conducted and were within specification but atypically high [redacted] (Exh. 3b5). The repeat test was conducted in the absence of a manufacturing investigation. [redacted] Exh. 3b6) states, "In order to explore an assignable cause for the assay results variation, a second repeat test was performed for experimental purposes by a different analyst using a different column...and instrument...It was carried out on new standards and sample preparations before the samples were weighed, the capsule powder was properly ground using a mortar and pestle (Exh. 3b6 p.2). The assay results for the second repeat test were [redacted] Although experimental testing was also done to evaluate the analytical method and laboratory techniques (intact capsules, grinding capsule powder, glass mortar, alternate diluent) and resulted in even higher assay values as documented in an addendum to [redacted] Exh. 3b1 pp. 8-22) dated [redacted] and [redacted] (Exh. 3b6), dated 12/19/07, no root cause was identified for the high assay at [redacted]. Although lot# 5436A1 is an annual stability batch (Exh. 3b7), [redacted] "No other batches are impacted by this stability failure." (Exh. 3b6 p. 5) No field alert was filed at the time of inspection.

A second [redacted] out of specification result was obtained for [redacted] on 12/3/07 as documented in [redacted] (Exh. 3b8). The laboratory notebook (Exh. 3b9), the chromatograms for the original, remeasurement and repeat tests are attached as (Exh. 3b10). A draft QA investigation, [redacted] Exh. 3b11) was still incomplete at the time of inspection. There was no field alert filed. Ms. Lambridis indicated that approximately [redacted] lots remained on the market at the time of inspection. This product is a controlled substance with indications for "exogenous obesity" (Exh. 3b12). The firm also manufactures Phentermine Capsules 15mg and 37.5mg. Ms. Lambridis stated that all powder filled capsule formulations of Phentermine would be evaluated to determine the impact; however no additional information was provided prior to the exit meeting. The firm also produces Phentermine using a seed filled capsule formulation and tablet formulation, which are different from the powder filled capsules that were out of specification. The

B4

firm has not fully assessed the impact of the stability out of specification results. We were notified on 4/23/08 that the firm was voluntarily recalling all batches [redacted] of Phentermine Capsules 30mg on the market within expiry. No recall was initiated for the 15mg or 37.5mg Capsules which are also powder filled.

c. **Out of specification assay and impurity results were obtained on 11/13/07 for Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg, lot# 5683A1, at the [redacted] stability time point, [redacted] Homatropine HBr impurity result: [redacted] Out of specification impurity results were also obtained on 12/26/07 during the testing of Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg, lot# 60437A1, an annual stability lot, at the [redacted] The Quality Assurance investigations were not completed and there was no evaluation of the [redacted] batches remaining on the market at the time of inspection.**

The laboratory [redacted] stability time point. revealed that out of specification assay results (low) and out of specification Homatropine HBr impurity results (high) were obtained: [redacted] and unknown impurity [redacted] (Exh. 3c1). The laboratory notebook (Exh. 3c2) and the chromatograms of the initial test, remeasurement and repeat test are included as Exhs. 3c3, 3c4, 3c5. The out of specification results were obtained on 11/13/07; however at the time of inspection both an addendum to the laboratory investigation [redacted] (Exh. 3c6) and the QA investigation report [redacted] (Exh. 3c7) were in draft. We noted that an NDA Field Alert was filed on 11/16/07 and included out of specification assay, dissolution, and impurities. The dissolution results were not included in OOSN 07-149 (Exh. 3c1) but were documented as part of the draft QA investigation [redacted] (Exh. 3c7). The dissolution results were as follows: Hydrocodone Bitartrate: [redacted] Homatropine Methylbromide: [redacted] Stability specifications are provided as Exh. 3c23.

An investigation plan for Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg, lot# 5683A1 dated 11/15/07 (Exh. 3c8) indicated that an evaluation of retention samples, an evaluation of the impurity test method, and an evaluation of all stability data for the products and a document review would be conducted. The results of the plan were not compiled, reviewed or approved at the time of inspection. Additionally, a QA interim report requesting an extension to the QA investigation time was drafted 3/19/08 with a target completion date of 4/30/08 (Exh. 3c9).

Out of specification impurity results were also obtained on 12/26/07 during the testing of Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg, lot# 60437A1, an

B4

annual stability lot, at the [redacted] RH stability time point, (unknown impurities [redacted] as documented in [redacted] (Exh. 3c10). The laboratory notebooks (Exh. 3c11) and chromatograms for initial testing for assay and related substances for Homatropine Methylbromide (Exh. 3c12), initial testing for related substances for Hydrocodone Bitartrate (Exh. 3c13), and repeat testing for related substances for Homatropine Hydrobromide (Exh. 3c14) were collected. A draft addendum to [redacted] (Exh. 3c15) confirmed the results and established no root cause for the out of specification results. A draft QA investigation into the 18-month impurity failures for lot# 60437A1 was initiated 12/27/07, but remained incomplete at the time of inspection. (Exh. 3c16) The draft states, "The batch in question is a stability batch that expires June 2008. Stability data for this product will be reviewed to determine the status of current batches on the market. The investigation will also review the current test method of analysis and the identity of the unknown impurity peak." There were three interim timeframe extensions issued for the QA investigation [redacted] 2/13/08 and 3/19/08, respectively (Exh. 3c17). Despite the two stability failures, there was no evaluation of the product risk based on the unknown impurities or the out of specification assay and dissolution results.

Ms. Lambridis acknowledged the failure of the Quality Unit to complete the investigation in a timely manner and evaluate the product on the market. She stated that although the investigations were not completed, reviewed and approved, some additional work had been done. She contacted Swapan Roychowdhury, Director Quality Control and Guarang Pandya, Group Leader, Analytical R&D. They stated that the analytical method was being re-evaluated and provided a report, [redacted] (Exh. 3c18). [redacted] provided as Exh. 3c19.

In the first [redacted] the unknown peaks were observed at retention times of approximately [redacted] minutes and [redacted] minutes in testing of [redacted] The known impurity peak [redacted] was observed at [redacted] minutes (Exh. 3c18 p. 2). The assay result for [redacted] one of two active ingredients was [redacted] avg [redacted] In the second OOS investigation, [redacted] the unknown out of specification peaks were observed with retention times of [redacted] minutes, [redacted] minutes, and [redacted] minutes in testing of Hydrocodone related substances (Exh. 3c18 p. 2).

In discussions with Mr. Roychowdhury and Mr. Pandya, it was explained that there are two separate analytical methods for the [redacted] and [redacted] When filed in [redacted] unknown impurities were calculated against the area of the smaller active peak [redacted] However, it was determined that one of the "unknown impurities" was originally thought to be part of the placebo/solvent front. The method directed the analyst to disregard the peaks prior to [redacted] retention time. Only when the peak began to increase in size over time, did they begin to evaluate it. The peak was later identified by a contract analytical laboratory [redacted] to be [redacted] (Exh. 3c20). An undated toxicity calculation for [redacted] was provided during the inspection (Exh. 3c21). Another two "unknown impurities" observed on the [redacted] chromatograms were

84

determined to be a degradants of Hydrocodone Bitartrate. They were being miscalculated against [redacted] Scott Talbot, Director Quality Assurance U.S Research and Development, Actavis South Atlantic, stated that the two existing methods are conducted at different wavelengths. The firm plans to file a single method which was developed in R&D and is being validated. We discussed the lack of assurance that the filed methods were stability indicating and the lack of documented information regarding the unknown impurities and their potential risks.

Ms. Lambridis notified us that following further evaluation by the laboratory for [redacted] was determined by Jisheng Zhu, Manager Finished Product and Stability Testing and Swapan Roychowdhury, Director Quality Control, the assay and dissolution out of specification results could not be overcome by the investigations and were therefore confirmed. Additionally, there was no assurance that all impurity issues were resolved or that the current analytical methods could adequately evaluate product quality. New Jersey District Recall Coordinator was notified on 4/23/08 that [redacted] of Hydrocodone Bitartrate and Homatropine Methylbromide Tablets were being voluntarily recalled from the market (Exh. 3c22).

d. **Out of specification assay results were obtained on 12/4/07 for Amantadine Hydrochloride Capsules, USP, 100mg, lot# 60324A1, at the [redacted] They were confirmed by re-measurement and retest; however the laboratory and Quality Assurance investigations were not completed and approved. No evaluation of the [redacted] batches remaining on the market had been made at the time of the inspection.**

Draft laboratory [redacted] documents the out of specification assay results which were obtained on [redacted] stability time point [redacted] (Exh. 3d1). A draft addendum to [redacted] (undated, unsigned) was also provided (Exh. 3d2.) The draft addendum states that the, "root cause seems to be method related". (Exh. 3d2 p. 3) The laboratory notebook showing the original out of specification results was provided as Exh. 3d3 p. 8. Chromatograms for the initial, remeasurement and repeat tests are provided as Exhs. 3d4-3d6. A draft Quality Assurance investigation initiated 1/10/08 only listed the out of specification results and did not include other details (Exh. 3d7). Despite the confirmed out of specification stability results, two timeframe extensions for the QA investigation were approved by Quality Assurance on 2/8/08 and 3/19/08 (Exh. 3d8, 3d9). There were [redacted] batches remaining on the market at the time of inspection (Exh. 3d10).

We discussed the out of specification results with Swapan Roychowdhury, Director Quality Control. He stated that the current analytical method, [redacted] for assay and related substances (chromatographic purity) was a GC extraction method with flame ionization detection (Exh. 3d11). The method uses a packed column [redacted] with a temperature gradient run from [redacted] Quantitation is achieved using Naphthalene as an internal

84

standard. Naphthalene and Amantadine elute at about [redacted] respectively with a run time of [redacted] for related substances testing). Mr. Roychowdry stated that the extraction method was challenging to run and there were issues regarding both the extraction and internal standard. (See also FDA 483 observation 5e). Scott Talbot, Director Quality Assurance, U.S. Research and Development stated that they are in discussions regarding the method. He explained that the current methods for content uniformity, dissolution and assay of in-process blend samples are HPLC methods using a refractive index detector (**Exh. 3d11 pp. 10-15**). According to Mr. Talbot, Mr. Roychowdhury proposed some annual reportable changes to the current method for better extraction using chloroform; however there are also ongoing discussions regarding the use of the HPLC method for assay and continued use of the GC method for related substances. Mr. Roychowdhury provided a "Method Remediation Progress Report" (**Exh. 3d12**) which concludes that, "The ultimate goal is to develop a HPLC method which is applicable to both assay and related substances testing for Amantadine Hydrochloride Capsules, USP 100mg." Mr. Talbot stated that the assay and content uniformity can be done in the same run using the HPLC refractive index method. That method, however is not stability indicating and another method would be required for related substances. Four [redacted] were analyzed using the HPLC method and results were within specification (**Exh. 3d13**). We discussed the failure of the Quality Unit to respond to the out of specification results and remediate the method in a timely manner. The approach to resolving the analytical method issues has not been determined. Although all investigational activities focused on the analytical method, there was no documented manufacturing investigation into the confirmed stability out of specification results and no documentation of other areas evaluated to assess product quality and determine root cause.

e. On 2/8/08 and 2/27/08, the 2006 and 2007 annual stability batches were out of specification for the known degradant 2,6 dichlorophenylacetic acid during the testing of Guanfacine Tablets, USP, 1mg and 2mg. The product has a [redacted] expiry for both strengths. There was no completed QA investigation and no evaluation of the approximately [redacted] batches of [redacted] batches of 2mg Guanfacine Tablets, USP that were on the market at the time of inspection.

Packaged stability lot number (package size)	Strength	% 2,6 dichlorophenylacetic acid	Spec (%)	Stab. Station 25°C/60%RH	Date of OOS	Exhs.
[redacted]						
[redacted]						
[redacted]						

B 4

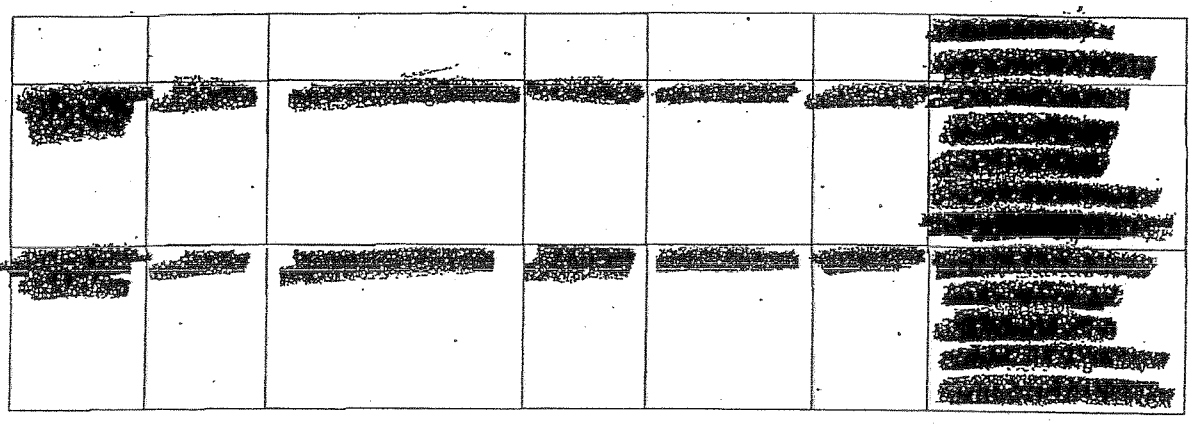

Exhibit references for the out of specification impurity data are listed in the last column of the table above. During discussions with Guarang Pandya, Group Leader, Analytical R&D, Actavis, (Taft Road, Totowa, NJ) a draft [redacted] was provided (Exh. 3e10). The historical data provided in the draft report ranges from [redacted] for the 1mg strength and [redacted] for the 2mg strength (Exh. 3e10 p. 3). The data for the batches cited was observed to be higher for both the 1mg and 2mg strengths and does not follow the documented trends; however, the firm notes, "The accrued stability data suggests that the finished product release and stability [redacted] is not realistic. Therefore Actavis is proposing to revise the specification for 2,6-Dichlorphenylacetic acid based on the stability data."

Investigator McCaffery discussed the noted differences in the cited data as compared to historical batches and asked if investigations into the process and raw materials were conducted to determine root cause for the differences. No documentation was provided. I, Investigator McCaffery requested information on the safety of the compound and was provided a report from a contractor stating, "There are no published data on the biological effects [redacted] in animals. It is used in the synthesis of guanfacine and is also a minor metabolite which is excreted in feces." (Exh. 3e11). The justification report for the change in specifications suggests (Exh. 3e10 p. 5):

Related Substances	Existing Spec. for Finished Product and Stability	Proposed Spec. for Finished Product	Proposed Spec. for Stability
2,6-dichlorophenylacetic acid	[redacted]	[redacted]	[redacted]
Total Known and Unknown Impurities	[redacted]	[redacted]	[redacted]

We also noted during the inspection that additional out of specification results for the degradant 2,6-

84

dichlorophenylacetic acid were obtained on 11/22/07 for lot#s 5393A1 and 5393A2 at the 24-month [redacted] (Exhs. 3e12). A draft QA investigation [redacted] was initiated on 12/11/07 and included no details of the investigation (Exh. 3e13). No field alert was filed for the out of specification stability results [redacted] notes that the lot was tested at [redacted] instead of at the 24 month expiry. We discussed the failure of the Quality Unit to investigate and to respond to the out of specification results in a timely manner with Ms. Lambridis. The firm originally committed to recalling only the batches in which the data could not be explained; however they later determined that approximately [redacted] Guanfacine Tablets, USP would be voluntarily recalled (Exh. 3e14).

f. **On 1/4/08, an out of specification stability result was received for the known degradation product, Mirtazapine N-oxide (MTZNO), during the testing of Mirtazipine Orally Disintegrating Tablets, 15 mg Lot 60794A1 at the [redacted] On 2/26/08, a second set of out of specification results for MTZNO was obtained during the testing of Mirtazipine Orally Disintegrating Tablets, 15 mg and 30 mg stability lot#s: 70279A1 (15 mg 9-month) [redacted], and 70421A1 (30 mg 6-month) [redacted] There was no completed QA investigation and no evaluation of the approximately [redacted] batches of 15mg and 7 batches of 30mg Mirtazapine Orally Disintegrating Tablets remaining on the market at the time of the inspection:**
(It was noted following the inspection that the laboratory raw data was obtained 1/3/08, instead of 1/4/08. [redacted] laboratory investigation was initiated on 1/4/08.)

Laboratory investigation [redacted] documents an out specification stability result for the degradation product, Mirtazapine N-oxide (MTZNO), during the testing of Mirtazapine Orally Disintegrating Tablets, 15 mg Lot 60794A1 at the [redacted] stability time point [redacted] was obtained 1/3/08 (Exh. 3f1). A draft addendum to [redacted] states that no laboratory assignable cause was identified (Exh. 3f2). The laboratory notebook was provided as Exh. 3f3 and chromatograms for initial (Exh. 3f4), remeasurement (Exh. 3f5), repeat test by original analyst (Exh. 3f6), repeat test by second analyst (Exh. 3f7), and remeasurement of repeat test by original analyst (Exh. 3f8). A timeframe extension for [redacted] was approved by QA with an "estimated due date" of 4/10/08, although the stability out of specification result was obtained 1/3/08 (Exh. 3f9).

Laboratory investigation [redacted] documents a second set of out of specification results for the degradation product, Mirtazapine N-oxide (MTZNO), during the testing of Mirtazapine Orally Disintegrating Tablets, lot#s: 70279A1 [redacted] and [redacted] (Exh. 3f10). An addendum to [redacted] was provided and concludes, "no laboratory related assignable cause was identified." (Exh. 3f11) The laboratory notebook (Exh. 3f12) and chromatograms for initial (Exh. 3f13), remeasurement (Exh. 3f14), and repeat testing (Exh. 3f15) are provided. At the time of inspection a draft one page QA investigation was provided (Exh. 3f16). It only included the out of specification data and did not include additional investigative information.

B4

During the inspection, Mr. Talbot and Ms. Lambridis stated that there was a potential "material related issue" and packaging issues due the blister packaging for the product; however no manufacturing investigation was provided to explain the potential source(s) of the OOS results. An updated draft of the [redacted] was provided near the end of the inspection (Exh. 3f17). It includes suspected root causes to be investigated for hold time of the blend, MTZNO increases in oxidative conditions, presence of increased levels of moisture causing degradation, and product formulation. Approximately [redacted] Mirtazapine Orally Disintegrating Tablets were on the market at the time of the inspection (Exh. 3f18). The draft report also notes that all lots are being voluntarily recalled and the manufacturing Master Production Record is being placed on hold and will remain on hold until, "these manufacturing issues are resolved." (Exh. 3f17 p. 3) Although the investigations discuss 15mg and 30mg strengths, the voluntary recall also includes the 45mg strength due to the similarities of the product formulations and packaging. A list of the 45mg lots on the market within expiry was provided as Exh. 3f19.

A [redacted] was previously submitted, 9/4/07 seeking approval to change the finished product specifications for [redacted] and for each unknown impurity from [redacted] (Exh. 3f20 p. 3). CDER responded 11/20/07 that a prior approval supplement was required (Exh. 3f20 pp. 1-2). No proposed change was filed for the stability specification for [redacted] which is [redacted] (Exh. 3f21) and was exceeded in the noted out of specification results above. We discussed the failure of the Quality Unit to assure that product quality issues were investigated in a timely manner. We also discussed the requests for changes in specifications despite the identified manufacturing/packaging issues. A draft analytical research investigation report was provided as Exh. 3f22 which discusses the formation of [redacted] and associated specifications. We were notified on 4/9/08 of the firm's intentions to voluntarily recall all batches on the market within expiry.

g. **Out of specification results for a known impurity, methoxysulphamide, [redacted] were obtained for Glyburide (micronized) Tablets, 1.5mg, lot#60164A1 at the [redacted] stability time point on 10/3/07. The Quality Assurance Director in QA investigation [redacted] indicated that the only other batch on the market, 70200A1, (a stability batch), is [redacted] however; in the same report, it notes, [redacted] Out of specification stability results for the known impurity, methoxysulphamide, [redacted] were again obtained on 3/26/08 for Glyburide (micronized) Tablets, 3.0mg, lot# 60170A1 and 60170AQ, respectively at the [redacted] The Quality Assurance investigation remains incomplete. The impact of the out of specification stability results on the approximately [redacted] atches on the market at the time of inspection [redacted] was not evaluated.**

Laboratory investigation [redacted] documents the out of specification results for a known impurity, methoxysulphamide, [redacted] obtained for Glyburide (micronized) Tablets, 1.5mg, lot#60164A1 at the [redacted] stability time point on 10/3/07 (Exh. 3g1). The laboratory notebook (Exh. 3g2) and chromatograms (initial) (Exh. 3g3), remeasurement (Exh. 3g4), repeat testing (Exh. 3g5), repeat testing with original analyst (Exh. 3g6)

B4

were provided. Additional experimental chromatography was performed including: immediately injecting the sample preparation, sample prepared without sonication and testing of retention samples. We discussed the numerous marketed products that were being tested "experimentally" as part of the firm's investigations. We questioned the original method development activities to support the chosen analytical methods. Mr. Roychowdhury, Director Quality Control stated that a number of products required method remediation or reformulation. QA investigation [redacted] (Exh. 3g7) includes a draft, "Justification Report for Revised Limit of Glyburide Related Compound A (Methoxy Sulphamide)" for Glyburide (Micronized) Tablets, USP, 1.5mg, 3mg, and 6mg (Exh. 3g7 pp. 73-83). Although the draft provides historical data and data from testing innovator product to attempt to justify a change in specification, there was no documented discussion about the formulation, manufacturing or packaging processes to try to determine the reason for the out of specification results. A signed copy of the justification report was provided as Exh. 3g8. The Quality Assurance Director in QA investigation [redacted] indicated that the only other batch on the [redacted] (a stability batch), is "currently well within specifications" (Exh. 3g7 p. 6). The Quality Assurance Director, in the same report then notes, "Based on the investigation and recent data from R&D who tested the innovator product, our specifications are set too low for the 1.5mg product." (Exh. 3g7 p. 7) [redacted], dated 1/3/08 proposes widening the specification for related substances for the 1.5mg, 3mg, and 6mg strengths (Exh. 3g9):

Related Substance	Current Specification	Proposed Specification
Glyburide Related Compound A (Methoxy Sulphamide)	[redacted]	[redacted]
Total Known and Unknown Related Substances	[redacted]	[redacted]

Out of specification stability results for the known impurity, methoxysulphamide, [redacted] were again obtained on 3/26/08 for Glyburide (micronized) Tablets, 3.0mg, lot# 60170A1 [redacted] as documented in draft [redacted] (Exh. 3g10) and draft addendum to OOSN 08-066 (Exh. 3g11) which summarizes the data. The laboratory notebook (Exh. 3g12) and chromatograms (initial) (Exh. 3g13), remeasurement (Exh. 3g14), and repeat testing (Exh. 3g15) were provided. The incomplete QA investigation [redacted] (Exh. 3g16) states that, "the most probable cause of the OOS known impurity stability results is due to the storage conditions of the stability samples. This indicates that the Glyburide product is affected by temperature and storage conditions." (Exh. 3g16 p. 3). The impact of the out of specification stability results on the approximately [redacted] on the market at the time of inspection [redacted] was not evaluated (Exh. 3g17). Following our discussions, the firm voluntarily recalled all strengths of the product (1.5mg, 3mg, and 6mg). Ms. Lambridis stated that the [redacted] results obtained on 3/26/08, during the inspection, were unanticipated and that the 6mg strength would be voluntarily recalled also. There were approximately [redacted] trength on the market within expiry.

h. Out of specification assay results were obtained for Chlordiazepoxide [redacted] for Chlordiazepoxide and Clidinium Bromide Capsules 5mg/2.5mg, lot# 5553A3 (100's) on 8/3/07 at the [redacted] The lot has a 36 month expiry. A degradant was observed during assay testing but

B4

was not quantified. There are no impurity specifications for the product on stability. A retention sample that was not maintained at [redacted] was used to retest the batch and was in specification, however the Quality Unit approved a protocol to test additional retention samples at expiry on 10/10/07, which resulted in three additional out of specification assay result for Chlordiazepoxide at 36 months; [redacted] Approximately [redacted] batches with 36 month expiry and 28 batches with 24 month expiry remained on the market at the time of inspection.

Note: At the exit meeting, Ms. Lambridis notified us of an error in the number of batches on the market within expiry. The total number of batches on the market within [redacted] Four batches had [redacted] and the other [redacted]

Laboratory [redacted] documented the out of specification assay results that were obtained for Chlordiazepoxide [redacted] in Chlordiazepoxide and Clidinium Bromide Capsules 5mg/2.5mg, lot# 5553A3 [redacted] stability time point. The lot has a 36 month expiry. (Exh. 3h1) The laboratory notebook is provided as Exh. 3h2. A representative chromatogram is contained in the QA investigation report [redacted] (Exh. 3h3 p. 36). A peak is observed between the two active peaks on the chromatogram at an approximate retention time of [redacted] The additional peak was not quantified. The laboratory investigation indicated, "lower assay was attributed to the degradation of chlordiazepoxide". (Exh. 3h1 p. 6) Rather than remeasuring and retesting the product as per [redacted] (Exh. 3h4), the retention sample for the lot, which was not maintained at [redacted] was used for a "retest". The assay results were [redacted] (Exh. 3h5). [redacted] stated that the former revision of the SOP allowed for laboratory supervision to "individually determine" the investigative steps for each occurrence and then have them approved by the QC Director (Exh. 3h4 p. 5). In this case, he stated that the product degradation was confirmed and the retention sample testing was conducted to evaluate whether the storage conditions had caused the degradation of the product. He noted it was considered a confirmed stability failure despite the acceptable results for the retention sample of that lot. The chromatograms for the assay testing of the retain sample, lot# 5553A3 were provided (Exh. 3h6). A contract laboratory, M-Scan evaluated the impurity peak and determined that it was chlordiazepoxide Related Compound A, a degradant of Chlordiazepoxide HCl (Exh. 3h7 p. 8). No evaluation of the degradant or the impact of the subpotent product due to the degradation was provided.

An additional protocol for Chlordiazepoxide HCl and Clidinium Bromide Capsules Retain Batch Testing Surveillance Protocol, dated 10/10/07 (Exh. 3h8) revealed that three additional lots tested at expiry (36 months) were out of specification for assay of Chlordiazepoxide. The out of specification lots included: lot# 4753A3, assay avg. [redacted] (Exh. 3h9).

Because the degradant was not quantified, we requested the stability specifications for impurities for

84

the product. Ms. Lambridis stated that there were no impurity specifications for the product on stability. The product does not have an approved application and was discontinued by the firm; however, [redacted] remained on the market within expiry. [redacted] expiry and the remaining [redacted] (Exh. 3h10). New Jersey District Recall Coordinator was notified that the firm was voluntarily recall the product on 4/9/08. This FDA 483 observation led to the finding that approximately [redacted] produced by the firm did not have impurity specifications on stability (Exh. 3h11). The stability specifications for Chlordiazepoxide and Clidinium Bromide Capsules, USP is provided as Exh. 3h12. (See also FDA 483 observation 5b). New Jersey District Recall Coordinator was also notified on 5/19/08 of the voluntary recall of the [redacted] for which impurity testing is not conducted on stability.

i. **Out of specification (low) assay results for Folic Acid were obtained for the prescription vitamin Multiret Folic Tablets 500mg, lot# 70607A1 (blister pack) at the [redacted] point on 1/8/08 [redacted] Out of specification assay results for Folic Acid were also obtained for lot# 70065A1 (blister pack) at the [redacted] stability time point on 2/26/08 [redacted] There was no completed QA investigation and no evaluation of the approximately [redacted] batches on the market at the time of inspection.**

Laboratory [redacted] documents the out of specification (low) assay results for Folic Acid that were obtained for the prescription vitamin Multiret Folic Tablets 500mg, lot# 70607A1 (blister pack) at the [redacted] RH stability time point on [redacted] (Exh. 3i1). The laboratory notebook (Exh. 3i2) and chromatograms (initial) (Exh. 3i3), remeasurement (Exh. 3i4), and retest (Exh. 3i5) were provided. An addendum to [redacted] ated 3/25/08 concluded that there was no laboratory assignable cause and that a full scale QA investigation [redacted] was being initiated (Exh. 3i6). A one page draft containing the results from the OOS report was provided as [redacted] Exh. 3i7). Two timeframe extensions were written by QA on 2/8/08 and 3/19/08 with estimated completion dates of 3/6/08 and 4/30/08, respectively (Exh. 3i8).

In the interim, a second out of specification assay result for Folic Acid was obtained for lot# 70065A1 (blister pack) at the [redacted] as documented in OOSN 08-042 (Exh. 3i9). The laboratory notebook (Exh. 3i10), chromatograms (initial) (Exh. 3i11), remeasurement (Exh. 3i12), and repeat testing (Exh. 3i13) were provided. A review of manufacturing documentation on 2/16/08 was conducted as (Exh. 3i14), and the Folic Acid was being evaluated as a potential source of the out of specification results; however at the time of inspection, the laboratory had confirmed the OOS results in an addendum to [redacted] (Exh: 3i15). A draft QA investigation was opened, but contains no investigational findings (Exh. 3i16).

This prescription product was marketed without an approved application (See the "PRESCRIPTION PRODUCTS WITHOUT APPROVED APPLICATIONS" section of this report: There is no

B4

evaluation of impurities on stability for the product as per the stability specifications (Exh. 3i17). There was no risk assessment for the out of specification low assay results for Folic Acid, however approximately 7 batches remained on the market at the time of inspection (Exh. 3i18). New Jersey District Recall Coordinator was notified on 4/4/08 that the firm was voluntarily recalling all lots within expiry from the market (Att).

j. **Out of specification (high) assay results for Thiamin Mononitrate were obtained for the pediatric prescription vitamin Multi Vita Bets with 1.0 mg Fluoride and Iron Chewable Tablets, lot# 70602A1 (100's) at the [redacted] stability time point on 11/22/07 [redacted]. Investigation [redacted] revealed that a calculation error in the analytical method occurred in which test results were calculated and reported as Thiamin Mononitrate; however the label claim was for Thiamin. Recalculation resulted in assay results within specification for stability batch 70602A1. Recalculations were not conducted until approximately [redacted] months later for [redacted] formulations of Multi Vita Bets containing Thiamin to evaluate the impact of the error. [redacted] finished product lots, (Multi Vita Bets, 0.5mg F and Fe Chewable Tablets, lot# 60642A, 61093A, Multi Vita Bets, with 1.0mg F Tablets 60345A, Multi Vita Bets with 0.25mg F Chewable Tablets 60337A), and four stability lots, (Multi Vita Bets with 0.25mg F Chewable Tablets 60226AQ, Mutli Vita Bets with 0.5mg F Tablets 60259AQ, Multi Vita Bets, with 1.0mg F Tablets 60205A1, 60205A2), were out of specification (low) by recalculation for Thiamin. The remaining [redacted] prescription vitamins containing Thiamin had not been evaluated at the time of inspection.**

Laboratory investigation [redacted] documented out of specification (high) assay results for Thiamin Mononitrate for the pediatric prescription vitamin Multi Vita-Bets with 1.0 mg Fluoride and Iron Chewable Tablets, lot# 70602A1 [redacted] (Exh. 3j1). The laboratory notebook (Exh. 3j2) and chromatograms (initial) (Exh. 3j3), standard comparison (Exh. 3j4), and repeat testing (Exh. 3j5) were provided. The laboratory investigation, [redacted] concluded, "That an error in the calculation formula was the root cause for the OOS results obtained during the assay for water-soluble vitamins conducted for the [redacted] stability sample of lot 70602A1 (Multi-vita Bets w/1.0 mg Fluoride and Iron Chewable Tabs). Therefore the recalculated results for the initial and repeat test met the required specifications and the average of the initial and repeat test will stand as the valid result of record." (Exh. 3j1 p. 3) The investigation [redacted] revealed that a calculation error in the analytical method occurred in which test results were calculated and reported as Thiamin Mononitrate; however the label claim was for Thiamin. Recalculation resulted in assay results within specification for stability batch 70602A1; but did not evaluate all other lots or products containing Thiamin.

Approximately two months later, on 1/17/08, a planned deviation was written to recalculate the Thiamin results for all Multi-vita Bets formulations (Exh. 3j6). Data summary tables were used to recalculate the data using a molecular weight conversion [redacted] (Exh. 3j7). [redacted]

B4

stated that the results were erroneously reported approximately [redacted] The assay specification for [redacted] (Therefore all datapoints less than approximately [redacted] that were initially reported would be out of specification for low assay). As a result of the recalculation, four finished product lots, (Multi Vita-Bets, 0.5mg F and Fe Chewable Tablets, lot# 60642A, 61093A (Exh. 3j8), Multi Vita-Bets, with 1.0mg F Tablets 60345A (Exh. 3j9) , Multi Vita-Bets with 0.25mg F Chewable Tablets 60337A (Exh. 3j10), and four stability lots, (Multi Vita-Bets with 0.25mg F Chewable Tablets 60226AQ (Exh. 3j11), Multi Vita-Bets with 0.5mg F Tablets 60259AQ (Exh. 3j12), Multi Vita-Bets, with 1.0mg F Tablets 60205A1, 60205A2 (Exh. 3j13), were out of specification (low) for assay of Thiamin.

A draft QA investigation [redacted] discusses the need to correct for the calculation error for Thiamin (Exh. 3j14). The impact of the deviation in the draft QA investigation states, "Since these are non-ANDA products, and the assay results would fall below specification, there is no significant impact as a result of this deviation." (Exh. 3j14) A timeframe extension for the QA investigation was written on 3/20/08, during the inspection and extended the completion date to [redacted] (Exh. 3j15).

Investigator Zielny inquired whether other products contained Thiamin and if so, were they evaluated. [redacted] stated that although the five Multi-vita Bets formulations were evaluated; they had not considered other products (See FDA 483 observation 6d). [redacted] later reported that 10 additional products contained Thiamin and would have to be evaluated. [redacted] also informed us during the inspection that the labeled amount of Thiamin or Thiamin Mononitrate would have to be evaluated as well as the formulation calculations for each product. A table included the routine manufacturing overages, the label claim, the formulation and method calculation was generated and provided during the inspection (Exh. 3j7). A representative example of the analytical method [redacted] (Exh. 3j16) and a formula page from a Master Production Record for Multi Vita-Bets with 1.0mg Fluoride Chewable Tablets were collected (Exh. 3j17).

These pediatric prescription vitamins were marketed without an approved application (See the "PRESCRIPTION PRODUCTS WITHOUT APPROVED APPLICATIONS" section of this report. We were notified on 4/9/08 that all lots of Multi-vita Bets Tablets, 0.25mg, 0.5mg, and 1.0mg were being voluntarily recalled. On 4/22/08, in a letter from Ms. Lambridis, a commitment to "cease distribution and manufacture of DESI products." (Exh. 13) The New Jersey District Recall Coordinator was notified on 5/19/08 that the firm was also voluntarily recalling approximately [redacted] additional prescriptions products (Exh. 3h11) which do not have impurity specifications on stability. The list to be recalled includes a number of the Thaimin containing products such as Prenatal Plus with 27mg Iron Tablets, Vitaplex Tablets, and Vitacon Forte Capsules.

k. **Out of specification (low) assay results for Acetaminophen and Dichloralphenazone were obtained for Amidrine Capsules, lot# 50638A1, an annual stability lot, at the [redacted] tability time point [redacted] In a repeat test conducted by a second analyst, the Acetaminophen and Dichloralphenazone results were within specification but "borderline"; however the assay results of the third active ingredient, Isometheptene Mucate were out of specification**

B4

[redacted] There was no completed QA investigation and no evaluation of the approximately [redacted] lots on the market.

Laboratory [redacted] documented the out of specification (low) assay results for Acetaminophen and Dichloralphenazone were obtained for Amidrine Capsules, lot# 50638A1, an annual stability lot, at the [redacted] (Acetaminophen assay [redacted] Dichloralphenazone assay [redacted] (Exh. 3k1). The laboratory notebook (Exh. 3k2), chromatograms (initial) (Exh. 3k3), remeasurement (Exh. 3k4), and repeat testing by a second analyst were collected, (Exhs. 3k5), 3k6). Although the remeasurement confirmed the OOS for Acetaminophen and Dichloralphenazone, the repeat test by a second analyst did not, but yielded "borderline" results for Acetaminophen [redacted] documented in OOSN 07-132 addendum (Exh. 3k1 p. 6, 8). A repeat test, conducted by a second analyst, was out out of specification for assay of Isometheptene Mucate (IMM) [redacted] which was confirmed by remeasurement. The laboratory notebook (Exh. 3k7) and chromatograms (Exhs. 3k8, 3k9) were provided. Despite the out of specification stability results for the annual stability batches, a draft QA investigation [redacted] (Exh. 3k10) indicates, "There is no impact on the subject batch since the batch expired in July 2007. Additionally, the Amidrine product has been discontinued." It was also noted in our review of the data that dissolution results for IMM ranged from [redacted] for this batch (Exh. 3k11). Further, the product has no stability specifications for impurities (Exhs. 3h11, 3k12). There was no evaluation of the approximately [redacted] on the market (Exh. 3k13).

This prescription product was marketed without an approved application (See the "PRESCRIPTION PRODUCTS WITHOUT APPROVED APPLICATIONS" section of this report). New Jersey District was notified on 4/9/08 that the [redacted] were being voluntarily recalled.

The numerous stability out of specification results were discussed throughout the inspection with Ms. Lambridis and in meetings with the firm's upper management. We stated that the response to the results was reactive based on our inspectional findings. It did not assure us that the firm's own Quality Unit and Quality System could identify and address product quality issues in a timely manner. We acknowledged the improvements in the laboratory such as the use of audit trails, independent data reviews, and notification to the Quality Unit of the out of specification results. We stated that the manufacturing and Quality Assurance investigations were not timely or were not conducted. We also acknowledged the firm's explanation that many products were placed in ICH stability conditions for the first time in 2005 which may have contributed to the numerous out of specification results. There is no assurance that other products which were not reviewed during our inspection will not have similar issues. Risk assessments were not conducted for the products which remain on the market or the products which are retained in the distribution centers that were made with the oversight of the same Quality Unit. At the exit meeting, I, Investigator McCaffery and Supervisory Investigator Harlan reiterated our concern for other products which were not evaluated as part of our inspection. During the exit meeting discussions, Mr. Wessman acknowledged the need

B4

for immediate and timely corrective action. He provided verbal and written commitments as documented in "ADMINISTRATIVE DATA", "GENERAL DISCUSSIONS WITH MANAGEMENT" and "VOLUNTARY CORRECTIONS" sections of this report.

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:
Observation 3a: 3a1-3a21
Observation 3b: 3b1-3b12
Observation 3c: 3c1-3c23
Observation 3d: 3d1-3d13
Observation 3e: 3e1-3e14
Observation 3f: 3f1-3f22
Observation 3g: 3g1-3g17
Observation 3h: 3h1-3h12
Observation 3i: 3i1-3i18, Att
Observation 3j: 3j1-3j17, 13, 3h11
Observation 3k: 3k1-3k13

OBSERVATION 4

Determinations of conformance to appropriate written specifications for acceptance are deficient for in-process materials.

Specifically,

a. **Although three out of specification results were obtained for blend uniformity at the "Right-Top" sample location for Digoxin Tablets 0.125 mg, lot#s 70148A (OOSN07-016), 70207A (OOSN07-022), and 70770A (OOSN07-116) on 2/20/07, 3/14/07 and 9/29/07; no manufacturing investigations were conducted. Additional samples were used to retest the blend and were reported. Lot# 70207A1 was released on 6/7/07 and lot# 70770A1 was released on 11/30/07 by the Quality Unit. Lot# 70148A was not released due to atypical content uniformity results.**

In reviewing the 2007 Annual Product Review for Digoxin Tablets 0.125 mg, I, Investigator Zielny noted that three of the five OOS Investigations were initiated due to out of specification results in blend uniformity testing (Exh. 4a1). Upon reviewing the three OOS Investigations, namely [redacted] (Exh. 4a2) for batch # 70148A, [redacted] (Exh. 4a3) for batch # 70207A, and [redacted] for batch # 70770A (Exh. 4a4), I noted that all three batches failed to meet blend

84

uniformity specifications due to a low result at the same sample point. Specifically, out of specification results for blend uniformity were obtained due to low results received at the "Right-Top" sample location in the blend uniformity testing of Digoxin Tablets 0.125 mg lot #s 70148A on 2/20/07, 70207A on 3/14/07 and 70770A on 9/29/07. The blend uniformity test specifications for batch #s 70148A and 70207A were Individual: [redacted], RSD: NMT [redacted] and the specifications for batch # 70770A were Average: [redacted] RSD: NMT [redacted] (See FDA 483 observation 4C for further information regarding changes in blend uniformity testing specifications.) The results for the "Right-Top" sample for the above mentioned batches are as follows:

Batch [redacted] (Exh. 4a5)
Batch [redacted] (Exh. 4a6)
Batch [redacted] (Exh. 4a7)

When samples were pulled for blend uniformity testing, duplicate samples were taken from the same sample locations. The testing of the duplicate samples of [redacted] and [redacted] was performed and the results were reported. For [redacted], triplicate samples had been taken from the same locations for blend uniformity testing. Sample set-2 and set-3 were tested and were within specification. The results from all three sample sets were reported for batch # 70770A. No manufacturing investigations were conducted into the original failing results for any of the three batches.

The OOS Investigation regarding [redacted] indicated that "the blend is considered acceptable for further processing however as an additional measure, [redacted] additional samples will be taken to confirm the products uniformity and acceptability prior to release to the market." A planned deviation, [redacted] (Exh. 4a8) was initiated in order to request an additional [redacted] throughout compression of the batch for content uniformity testing. Although the additional content uniformity testing met specification, a final decision to reject batch # 70148A was made because "no root cause was identified and the content uniformity results were not conclusive". This decision to reject the batch can be seen on page 2 of Exh. 4a8. [redacted] Finished Product and Stability Testing explained that the inconclusive content uniformity results were referencing the fact that the original content uniformity testing went to the L-2 testing phase because the content uniformity testing of the first ten tablets resulted in an acceptance value of [redacted] whereas specification is [redacted] Exh. 4a9, p. 4). Exh. 4a9 shows the original content uniformity testing, the L-2 testing and the testing of the additional [redacted] as required by [redacted] The L-2 testing passed specification for acceptance value. [redacted] stated that the rejection of the batch was due to 1) the fact that original content uniformity testing went to stage-2 (L-2) testing and 2) A difference was observed between the results received during the original content uniformity testing and the results received for content uniformity testing of the additional [redacted] Lot # 70148A1 was rejected on 7/23/07 (Exh. 4a10), four months after the initiation of the planned deviation to perform additional content uniformity testing.

84

Batch # 70207A also had a planned deviation [redacted] associated with the batch in order to perform content uniformity testing on an additional [redacted] taken throughout compression. The additional samples met specifications and lot # 70207A1 was released for shipment on 6/7/07. Copies of the compression release, bulk product disposition form, batch record review and finished product release form are attached as **Exh. 4a11.**

Batch # 70770A did not have a planned deviation associated with the batch. No answer could be provided as to why the first two OOS blend uniformity investigations included provisions for additional content uniformity testing and this investigation failed to initiate a similar planned deviation. Lot # 70770A1 was released for shipment on 11/30/07, without additional content uniformity testing. Copies of the compression release, bulk product disposition form, batch record review and finished product release form are attached as **Exh. 4a12.**

b. **Out of specification in-process results were obtained for friability of start-up and compression composite samples for Methenamine Mandelate Tablets 1.0g, lot# 70662A on 10/12/07. Despite the in-process out of specification results the batch was released to the market on 2/5/08 by the Quality Unit.**

Laboratory [redacted] documents the out of specification in-process friability results for Methanimine Mandelate Tablets, USP 1.0 g **(Exh. 4b1).** QA investigation [redacted] revealed that the startup samples and the composite samples from the batch were collected and sent to the lab for friability testing; however the batch was completed and sent for coating prior to determining that there were friability failures ("broken tablets") for the startup and composite samples **(Exh. 4b2).** The other in-process and finished product testing met specifications **(Exh. 4b3);** however the manufacturing investigation only evaluated compression and did not evaluate raw materials, production of the blend, moisture or any other aspects which may have caused the friability failures. The batch was released despite the in-process failures **(Exh. 4b4).** The QA investigation notes that the batch did not have any issues of broken tablets during coating and met all other specifications. An interim report timeframe extension to [redacted] noted, "Product passed specs for hardness and has already been coated." **(Exh. 4b5).** The lot remains on the market and was not placed on stability. Mr. Talbot notes in the QA investigation that, "the primary function of performing friability check on the core tablets is to highlight any potential issues with breaking tablets during the film coating process." **(Exh. 4b2 p. 3).** We stated that the specification historically was met and that the investigation should evaluate the root cause of the OOS.

c. **Although approximately [redacted] products were "temporarily discontinued" due to blend and/or content uniformity issues, there was no scientific rationale provided for the change of in-process blend uniformity specifications from [redacted]**

During the inspection, we were provided with a list of products that have been temporarily discontinued **(Exh. 4c1).** The list includes "blend uniformity issues" as a reason for the temporary

84

discontinuation in the production of Betaxolol Tablets, USP 10 mg, Carisoprodol, Aspirin and Codeine Phosphate Tablets, USP 200mg/325mg/16mg, Chlor-timetron, Drixoral Cold & Allergy Extended Release Tablets and Hydrocodone Bitarttrate and Homatropine Methylbromide Tablets 5mg/1.5mg. Despite noted "blend uniformity issues", in-process blend uniformity specifications for many products were changed from [redacted] (*individual*) RSD NMT [redacted] (*average*) [redacted]. Current in-process blend uniformity specifications for the following products are listed at [redacted] (Average) [redacted] (Exh 4c2):

Betaxolol Tablets, USP 10 mg and 20 mg
Buspirone Hydrochloride Master Blend
Buspirone Hydrochloride Tablets, USP 30 mg
Carisoprodol, Aspirin & Codeine Tablets
Dantrolene Sodium Capsules, 25 mg, 50 mg and 100 mg
Digoxin Tablets, USP 0.125 mg and 0.25 mg
Dipyridamole Tablets USP, Master Blend
Hydromorphone Hydrochloride Tablets, USP 8 mg
Isradipine Capsules, USP 2.5 mg and 5 mg
Loxapine Capsules, USP 5 mg, 10 mg, 25 mg and 50 mg
Meloxicam Tablets 7.5 mg and 15 mg
Meperidine HCL Tablets, 50 mg and 100 mg
Mirtazapine Orally Disintegrating Tablets- Master Blend
Oxycodone Hydrochloride Tablets, USP 15 mg and 30 mg
Pentazocine Hydrochloride and Acetaminophen Caplets
Phendimetrazine Tartrate Tablets, USP 35 mg
Phentermine Hydrchloride Capsules, 15 mg and 30 mg
Quinaretic (Quinapril Hydrochloride and Hydrochlorothiazide) Tablets, 10/12.5 mg and 20/25 mg
Quinapril Hydrochloride Tablets, 5 mg, 10 mg, 20 mg and 40 mg
Rifampin Capsules, USP 300 mg
Trimethobenzamide Hydrochloride Capsules, USP 300 mg
Trimipramine Maleate Capsules, 25 mg, 50 mg and 100 mg
Ursodiol Capsules, USP 300 mg

The list of "temporarily discontinued products" also indicates that three of the five products with blend issues also had content uniformity issues. The products include: Betaxolol Tablets, USP 10mg, Chlor-Trimeton Tablets, and Drixoral Cold & Allergy Extended-Release Tablets (Exh. 4c1). However an "interim report fo[redacted] discusses blend uniformity issues with 17 batches and concludes that the "the recent trend of product blend failures in 2007 was attributed to the sample handling, the addition of slugging the blend samples and the testing of blends and was not due to a shift in manufacturing practices." (Exh. 4c3). No scientific rationale could be provided for

84

changing in-process blend specifications from [redacted]

In discussions with Mr. Talbot and Ms. Lambridis, we were told that a recent application [redacted] the mean results. RSD of all individual results [redacted] The Deficiency Letter from the agency, dated 7/2/07, indicated: "The acceptance criterion for Uniformity of Content for granulation blend (Blend Uniformity) should be revised to "the mean of all test results is [redacted] of the active ingredient with a [redacted] (Exh. 4c5 p. 3). A minor amendment was subsequently filed to revise the acceptance criterion for Blend Uniformity to state "the mean of all test results is [redacted] the target value (i.e. label claim) of the active ingredient with a [redacted] (Exh. 4c6 p.2).

Ms. Lambridis provided examples of other recent applications with blend uniformity specifications of [redacted]

Phendimetrazine Tartrate Tablets, USP 35 mg (approved 1/28/08) (ANDA 40-762) (Exh. 4c7)

Imipramine HCl Tablets USP, 10 mg (approved 2/28/08) (ANDAs 40-751, 50 mg, 40-752, 25mg and 40-753, 10 mg) (Exh. 4c8)

Buspirone HCl Tablets, USP 30 mg (approved 12/17/07) (ANDA 78-302) (Exh. 4c9 and 4c2 pp. 3-4)

According to the firm's FDA Telephone Record, a telephone conversation on 6/14/07 was held with a reviewer from CDER's Office of Generic Drugs. The call included discussions regarding the desire to change existing in-process specifications for blend uniformity fr[redacted] (Individual) [redacted] (Average or Mean) [redacted] (Exh. 4c10). The call was placed to see if this change was annual reportable. The reviewer confirmed with his supervision and in a follow-up call on 6/21/07, firm personnel were told that the change in in-process blend specifications from individual to average or mean was an annual reportable change.

We noted that in-process blend specifications differed from product to product. We discussed the need to provide scientific rationale and data to support the change in in-process specifications. We noted that, for example, that blend uniformity specifications for Drixoral Cold & Allergy Extended-Release Tablets, which are contract manufactured by Actavis, are currently [redacted] of Mean Value; [redacted] for both Dexbrompheniramine Maleate and Pseudophedrine Sulfate; however there is no range provided for the mean (Exh. 4c11). At the exit meeting, I, Investigator McCaffery reiterated the need to provide product specific data and scientific rationale to support changes in specifications.

d. Out of specification in-process blend uniformity testing of Oxycodone Tablets, 15mg, lot# 70164A was obtained on 3/3/07 [redacted]

84